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APPLICATION NUMBER: ***60/564,538***
FILING DATE: ***April 22, 2004***
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-16772	Type a plus sign (+) inside this box -->	+

INVENTOR(s)/APPLICANT(s)

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TITLE OF THE INVENTION (280 characters max)

BACE INHIBITORS

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ENCLOSED APPLICATION PARTS (*check all that apply*)

X	Specification	Number of pages	180		Small Entity Statement		
	Drawing(s)	Number of Sheets			Other (Specify)		

METHOD OF PAYMENT (*check one*)

	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT ($)	$160.00
X	The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

X No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE _____ Date 04 / 22 / 04

TYPED or PRINTED NAME ROBERT D. TITUS REGISTRATION NO. (*if appropriate*) 40,206

☐ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

"Express Mail" mailing label number EL 832954249 US Date of Deposit 4-22-04

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450.

QUEEN THOMAS _____
Printed Name Signature

BACE INHIBITORS

BACKGROUND OF THE INVENTION

Alzheimer's disease, characterized by cognitive and behavioral deterioration in its latter stages, has emerged as a significant social and financial concern. With a prevalence approaching 5.5% in the population above the age of 60, the cost for care of Alzheimer's disease patients has been estimated to be in excess of $100 billion annually. Although cholinesterase inhibitors are quite effective in reducing the symptoms of Alzheimer's disease, particularly when the disease is in its early phases, they are not at all effective in slowing or stopping the progression of the disease.

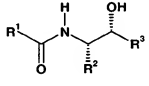
Neurofibrillary tangles and neuritic plaques are generally found in the brain regions associated with memory and cognition of those afflicted with Alzheimer's disease. These plaques are also found in the brains of individuals with Down's syndrome, Hereditary Cerebral Hemorrhage of the Dutch-Type, and other neurodegenerative disorders. The neuritic plaques are comprised primarily of amyloid β (Aβ) peptide, a neurotoxic and highly aggregatory peptide segment of amyloid precursor protein (APP). Aβ peptide is formed by the proteolytic cleavage of APP by β-secretase (BACE) followed by at least one subsequent C-terminal cleavage by γ-secretase. As such, inhibition of BACE is an attractive target for the treatment or prevention of Alzheimer's disease as well as other diseases characterized pathologically by amyloid plaques.

BACE is a member of the pepsin sub-family of mammalian aspartyl proteases and, like its substrate APP, is a type I transmembrane protein. BACE has been disclosed in the literature and is referred to also as "β-site APP-cleaving enzyme", "membrane aspartic protease of the pepsin family", "Asp-2", "β-secretase", "membrane-bound aspartic protease" and "Memapsin 2" (See: Ghosh, et al., Current Medicinal Chemistry, **9**(11), 1135-1144 (2002)). Two isoforms of BACE have been identified in humans, designated BACE1 and BACE2. It is believed that the BACE1 inhibitory activity is most important to inhibition of amyloid β (Aβ) peptide (Roggo, Current Topics in Medicinal Chemistry, **2**, 359-370 (2002)). Currently described BACE inhibitors are peptidomimetic transition state analogs, typically containing a hydroxyethyl moiety. Although many of these compounds are potent inhibitors of BACE, their high molecular

weights and low membrane permeability make them poor drug candidates. (See: Park and Lee, Journal of the American Chemical Society, **125**(52), 16416-16422 (2003)). Additional compounds described as BACE inhibitors are disclosed in WO 03/040096, WO 04/024081, and WO 04/0039034. Additional BACE inhibitors are necessary to provide treatments for A-β peptide mediated disorders such as Alzheimer's disease. The present invention provides new inhibitors of BACE.

BRIEF SUMMARY OF THE INVENTION

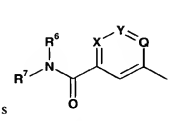
The present invention provides compounds of Formula I:



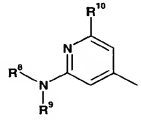
I

where:

R^1 is hydrogen, $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_1\text{-}C_6$ alkyl), $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkenyl), $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkynyl), $C_3\text{-}C_7$ cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, $C_1\text{-}C_6$ alkoxy, $C_3\text{-}C_7$ cycloalkoxy, and NR^4R^5, or



or



;

R^1 is

R^2 is $C_1\text{-}C_3$ alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

R^3 is piperidin-2-yl optionally substituted with one or two substituents independently selected from $C_1\text{-}C_6$ alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and $C_1\text{-}C_6$ alkyl, 1-($C_1\text{-}C_6$ alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydro-isoquinolin-3-yl optionally substituted with one or two substituents selected from halo

and C_1-C_6 alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo, or one or two substituents selected from hydroxy and fluoro;

X is CH, N, or N^+-O^-;

Y is CR^{11}, N, or N^+-O^-;

Q is CR^{12}, N, or N^+-O^-;

R^4 is hydrogen, C_1-C_6 alkyl, or phenyl;

R^5 is hydrogen, C_1-C_6 alkyl, phenyl, -C(O)(C_1-C_6 alkyl), or $-SO_2$(C_1-C_6 alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or C_1-C_6 alkyl;

R^9 is C_3-C_5 cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1,2}R^{16}$, $-NR^{17}SO_2R^{18}$, (C_1-C_3 alkoxy)-carbonyl, phenyl optionally substituted with halo, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with C_1-C_3 alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}; CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

R^{23} is hydrogen or methyl;

R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

R^{26} is methyl; or

R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring;

or a pharmaceutically acceptable salt thereof; provided that no more than one of X, Y, and Q may be N or N^+-O^-.

The present invention also provides a method of treating Alzheimer's disease in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention further provides a method of preventing the progression of mild cognitive impairment to Alzheimer's disease in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention also provides a method of inhibiting BACE in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention also provides a method for inhibiting β-secretase mediated cleavage of amyloid precursor protein comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention further provides a method for the inhibition of production of A-β peptide comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

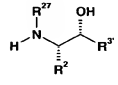
The present invention also provides a pharmaceutical formulation comprising a compound of Formula I, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

Furthermore, this invention provides the use of a compound of Formula I for the manufacture of a medicament for the treatment of Alzheimer's disease. This invention also provides the use of a compound of Formula I for the manufacture of a medicament for the prevention of the progression of mild cognitive impairment to Alzheimer's disease. The invention also provides the use of a compound of Formula I for the manufacture of a medicament for the inhibition of BACE. The present invention also provides the use of a compound of Formula I for the manufacture of a medicament for the inhibition of β-secretase mediated cleavage of amyloid precursor protein. The invention further provides the use of a compound of Formula I for the manufacture of a medicament for the inhibition of production of A-β peptide.

Additionally, this invention provides a pharmaceutical formulation adapted for the treatment of Alzheimer's disease. Furthermore, this invention provides a pharmaceutical formulation adapted for the prevention of the progression of mild cognitive impairment to Alzheimer's disease. This invention also provides a pharmaceutical formulation adapted for the inhibition of BACE.

Furthermore the present invention provides a pharmaceutical formulation adapted for the inhibition of β-secretase mediated cleavage of amyloid precursor protein. The present invention also provides a pharmaceutical formulation adapted for the treatment of conditions resulting from excessive production and/or reduced clearance of A-β peptide comprising a compound of Formula I or a pharmaceutically acceptable salt thereof in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents.

This invention also provides intermediates of Formula II:



II

where:

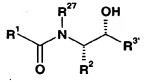
R^2 is C_1-C_3 alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

R^{27} is either hydrogen or a nitrogen protecting group;

$R^{3'}$ is piperidin-2-yl optionally substituted with one or two substituents independently selected from C_1-C_6 alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and C_1-C_6 alkyl, 1-(C_1-C_6 alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl optionally substituted with one or two substituents selected from halo and C_1-C_6 alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo or one or two substituents selected from hydroxy and fluoro; all substituted on the ring nitrogen adjacent to the point of attachment with variable R^{28};

R^{28} is either hydrogen or a nitrogen protecting group; or an acid addition salt thereof.

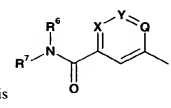
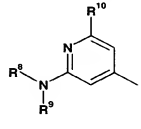
This invention further provides intermediates of Formula III:



III

where:

R^1 is hydrogen, (C_3-C_7 cycloalkyl)$_{0-1}$(C_1-C_6 alkyl), (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkenyl), (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, and NR^4R^5, or

R^1 is  or  ;

R^2 is C_1-C_3 alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

$R^{3'}$ is piperidin-2-yl optionally substituted with one or two substituents independently selected from C_1-C_6 alkyl, pyrrolidin-2-yl optionally substituted with p-

toluenesulfonyloxy or with one or two substituents independently selected from halo and C_1-C_6 alkyl, 1-(C_1-C_6 alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl optionally substituted with one or two substituents selected from halo and C_1-C_6 alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo or one or two substituents selected from hydroxy and fluoro; all substituted on the ring nitrogen adjacent to the point of attachment with variable R^{28};

X is CH, N, or N^+-O^-;

Y is CR^{11}, N, or N^+-O^-;

Q is CR^{12}, N, or N^+-O^-;

R^4 is hydrogen, C_1-C_6 alkyl, or phenyl;

R^5 is hydrogen, C_1-C_6 alkyl, phenyl, -C(O)(C_1-C_6 alkyl), or $-SO_2$(C_1-C_6 alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or C_1-C_6 alkyl;

R^9 is C_3-C_5 cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1-2}R^{16}$, $-NR^{17}SO_2R^{18}$, (C_1-C_3 alkoxy)-carbonyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with C_1-C_3 alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}; CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

R^{23} is hydrogen or methyl;

R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

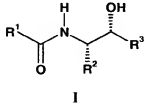
R^{26} is methyl; or

R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring;

R^{27} and R^{28} are either independently a nitrogen protecting group or one is hydrogen and the other a nitrogen protecting group;

or an acid addition salt thereof provided that no more than one of X, Y, and Q may be N or N^+-O^-.

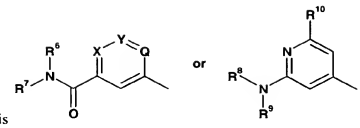
The present invention further provides a process for the preparation of a compound of Formula I:



I

where:

R^1 is hydrogen, $(C_3$-C_7 cycloalkyl$)_{0-1}(C_1$-C_6 alkyl), $(C_3$-C_7 cycloalkyl$)_{0-1}(C_2$-C_6 alkenyl), $(C_3$-C_7 cycloalkyl$)_{0-1}(C_2$-C_6 alkynyl), C_3-C_7 cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, and NR^4R^5, or



;

R^1 is

R^2 is C_1-C_3 alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

R^3 is piperidin-2-yl optionally substituted with one or two substituents independently selected from C_1-C_6 alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and C_1-C_6 alkyl, 1-(C_1-C_6 alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl optionally substituted with one or two substituents selected from halo and C_1-C_6 alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo, or one or two substituents selected from hydroxy and fluoro;

X is CH, N, or N^+-O^-;

Y is CR^{11}, N, or N^+-O^-;

Q is CR^{12}, N, or N^+-O^-;

R^4 is hydrogen, C_1-C_6 alkyl, or phenyl;

R^5 is hydrogen, C_1-C_6 alkyl, phenyl, -C(O)(C_1-C_6 alkyl), or $-SO_2$(C_1-C_6 alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or C_1-C_6 alkyl;

R^9 is C_3-C_5 cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1-2}R^{16}$, $-NR^{17}SO_2R^{18}$, (C_1-C_3 alkoxy)-carbonyl, phenyl optionally substituted with halo, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with C_1-C_3 alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}; CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and

methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

R^{23} is hydrogen or methyl;

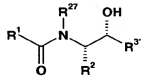
R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

R^{26} is methyl; or

R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring; provided that no more than one of X, Y, and Q may be N or N^+-O^-, comprising the steps of:

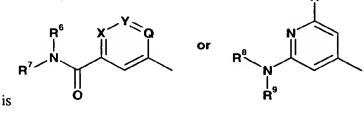
a) deprotecting a compound of Formula III:



III

where:

R^1 is hydrogen, $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_1\text{-}C_6$ alkyl), $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkenyl), $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkynyl), $C_3\text{-}C_7$ cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, $C_1\text{-}C_6$ alkoxy, $C_3\text{-}C_7$ cycloalkoxy, and NR^4R^5, or

R^1 is  ;

R^2 is $C_1\text{-}C_3$ alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

$R^{3'}$ is piperidin-2-yl optionally substituted with one or two substituents independently selected from $C_1\text{-}C_6$ alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and $C_1\text{-}C_6$ alkyl, 1-($C_1\text{-}C_6$ alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydro-isoquinolin-3-yl optionally substituted with one or two substituents selected from halo and $C_1\text{-}C_6$ alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo or one or two substituents selected from hydroxy and fluoro; all substituted on the ring nitrogen adjacent to the point of attachment with variable R^{28};

X is CH, N, or $N^+\text{-}O^-$;

Y is CR^{11}, N, or $N^+\text{-}O^-$;

Q is CR^{12}, N, or $N^+\text{-}O^-$;

R^4 is hydrogen, $C_1\text{-}C_6$ alkyl, or phenyl;

R^5 is hydrogen, $C_1\text{-}C_6$ alkyl, phenyl, $-C(O)(C_1\text{-}C_6$ alkyl), or $-SO_2(C_1\text{-}C_6$ alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or $C_1\text{-}C_6$ alkyl;

R^9 is $C_3\text{-}C_5$ cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1\text{-}2}R^{16}$, $-NR^{17}SO_2R^{18}$, ($C_1\text{-}C_3$ alkoxy)-carbonyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with $C_1\text{-}C_3$ alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}, CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

R^{23} is hydrogen or methyl;

R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

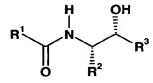
R^{26} is methyl; or

R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring;

R^{27} and R^{28} are either independently a nitrogen protecting group; or one of R^{27} and R^{28} is hydrogen and the other is a nitrogen protecting group; or an acid addition salt thereof, provided that no more than one of X, Y, and Q may be N or N^+-O^-; and

b) optionally treating the compound of Formula I with a pharmaceutically acceptable acid to form the corresponding pharmaceutically acceptable salt.

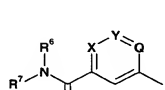
The present invention also provides a process for the preparation of a compound of Formula I:



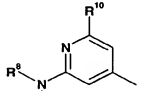
I

where:

R^1 is hydrogen, $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_1\text{-}C_6$ alkyl), $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkenyl), $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkynyl), $C_3\text{-}C_7$ cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, $C_1\text{-}C_6$ alkoxy, $C_3\text{-}C_7$ cycloalkoxy, and NR^4R^5, or



or



;

R^1 is

R^2 is $C_1\text{-}C_3$ alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

R^3 is piperidin-2-yl optionally substituted with one or two substituents independently selected from $C_1\text{-}C_6$ alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and $C_1\text{-}C_6$ alkyl, 1-($C_1\text{-}C_6$ alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydro-isoquinolin-3-yl optionally substituted with one or two substituents selected from halo and $C_1\text{-}C_6$ alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo, or one or two substituents selected from hydroxy and fluoro;

X is CH, N, or $N^+\text{-}O^-$;

Y is CR^{11}, N, or $N^+\text{-}O^-$;

Q is CR^{12}, N, or $N^+\text{-}O^-$;

R^4 is hydrogen, C_1-C_6 alkyl, or phenyl;

R^5 is hydrogen, C_1-C_6 alkyl, phenyl, -C(O)(C_1-C_6 alkyl), or $-SO_2$(C_1-C_6 alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or C_1-C_6 alkyl;

R^9 is C_3-C_5 cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1,2}R^{16}$, $-NR^{17}SO_2R^{18}$, (C_1-C_3 alkoxy)-carbonyl, phenyl optionally substituted with halo, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with C_1-C_3 alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}; CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

R^{23} is hydrogen or methyl;

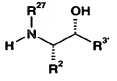
R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

R^{26} is methyl; or

R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring; provided that no more than one of X, Y, and Q may be N or N^+-O^-, comprising the steps of:

a) coupling a compound of Formula II:



II

where:

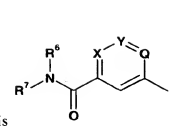
R^2 is C_1-C_3 alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

R^{27} is either hydrogen or a nitrogen protecting group;

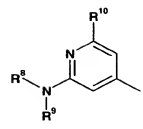
$R^{3'}$ is piperidin-2-yl optionally substituted with one or two substituents independently selected from C_1-C_6 alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and C_1-C_6 alkyl, 1-(C_1-C_6 alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydro-isoquinolin-3-yl optionally substituted with one or two substituents selected from halo and C_1-C_6 alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo or one or two substituents selected from hydroxy and fluoro; all substituted on the ring nitrogen adjacent to the point of attachment with variable R^{28};

R^{28} is either hydrogen or a nitrogen protecting group; or an acid addition salt thereof, with a carboxylic acid of formula R^1-COOH or equivalent thereof where:

R^1 is hydrogen, (C_3-C_7 cycloalkyl)$_{0\text{-}1}$(C_1-C_6 alkyl), (C_3-C_7 cycloalkyl)$_{0\text{-}1}$(C_2-C_6 alkenyl), (C_3-C_7 cycloalkyl)$_{0\text{-}1}$(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, and NR^4R^5, or



or



;

R^1 is

R^2 is C_1-C_3 alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

X is CH, N, or N^+-O^-;

Y is CR^{11}, N, or N^+-O^-;

Q is CR^{12}, N, or N^+-O^-;

R^4 is hydrogen, C_1-C_6 alkyl, or phenyl;

R^5 is hydrogen, C_1-C_6 alkyl, phenyl, -C(O)(C_1-C_6 alkyl), or $-SO_2$(C_1-C_6 alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or C_1-C_6 alkyl;

R^9 is C_3-C_5 cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1,2}R^{16}$, $-NR^{17}SO_2R^{18}$, (C_1-C_3 alkoxy)-carbonyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with C_1-C_3 alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}; CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

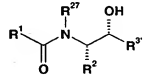
R^{23} is hydrogen or methyl;

R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

R^{26} is methyl; or

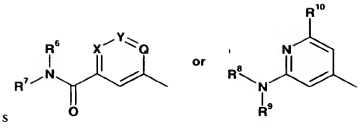
R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring; provided that no more than one of X, Y, and Q may be N or N^+-O^- to form the corresponding amide of Formula III:



III

where:

R^1 is hydrogen, $(C_3$-C_7 cycloalkyl$)_{0\text{-}1}(C_1$-C_6 alkyl), $(C_3$-C_7 cycloalkyl$)_{0\text{-}1}(C_2$-C_6 alkenyl), $(C_3$-C_7 cycloalkyl$)_{0\text{-}1}(C_2$-C_6 alkynyl), C_3-C_7 cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, and NR^4R^5, or



;

R^1 is

R^2 is C_1-C_3 alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

$R^{3'}$ is piperidin-2-yl optionally substituted with one or two substituents independently selected from C_1-C_6 alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and C_1-C_6 alkyl, 1-(C_1-C_6 alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl optionally substituted with one or two substituents selected from halo and C_1-C_6 alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo or one or two substituents selected from hydroxy and fluoro; all substituted on the ring nitrogen adjacent to the point of attachment with variable R^{28};

X is CH, N, or N^+-O^-;

Y is CR^{11}, N, or N^+-O^-;

Q is CR^{12}, N, or N^+-O^-;

R^4 is hydrogen, C_1-C_6 alkyl, or phenyl;

R^5 is hydrogen, C_1-C_6 alkyl, phenyl, -C(O)(C_1-C_6 alkyl), or $-SO_2$(C_1-C_6 alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or C_1-C_6 alkyl;

R^9 is C_3-C_5 cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1-2}R^{16}$, $-NR^{17}SO_2R^{18}$, (C_1-C_3 alkoxy)-carbonyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with C_1-C_3 alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}; CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and

methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

R^{23} is hydrogen or methyl;

R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

R^{26} is methyl; or

R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring;

R^{27} and R^{28} are independently either hydrogen or a nitrogen protecting group; or an acid addition salt thereof provided that no more than one of X, Y, and Q may be N or N^+-O^-;

b) optionally deprotecting an amide of Formula III; and

c) optionally treating the compound of Formula I with a pharmaceutically acceptable acid to form the corresponding pharmaceutically acceptable salt.

DETAILED DESCRIPTION OF THE INVENTION

The general chemical terms used in the formulae above have their usual meanings. For example, the term "C_1-C_6 alkyl" includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, and hexyl moieties. The term "C_3-C_7 cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl moieties. The term "C_2-C_6 alkenyl" includes ethenyl, prop-1-en-3-yl, prop-1-en-2-yl, 2-methylprop-1-en-1-yl, and the like. The term "C_2-C_6 alkynyl" includes ethynyl, prop-1-yn-3-yl, prop-1-yn-1-yl, 4-methylpent-2-yn-1-yl, and the like. "Halo" includes fluoro, chloro, bromo, and iodo.

The term "C_1-C_6 alkoxy" is a C_1-C_6 alkyl group bonded to an oxygen atom and includes methoxy, ethoxy, isopropoxy, tert-butoxy, and the like. The term "C_3-C_7 cycloalkoxy" is a C_3-C_7 cycloalkyl group bonded through an oxygen atom and includes cyclopropoxy, cyclobutoxy, cyclopentoxy, and the like.

The term "$(C_3$-C_7 cycloalkyl$)_{0\text{-}1}(C_1$-C_6 alkyl)" is taken to mean a C_1-C_6 alkyl moiety optionally substituted with one C_3-C_7 cycloalkyl moiety at any available carbon atom in the C_1-C_6 alkyl moiety. Similarly, "$(C_3$-C_7 cycloalkyl$)_{0\text{-}1}(C_2$-C_6 alkenyl)" and "$(C_3$-C_7 cycloalkyl$)_{0\text{-}1}(C_2$-C_6 alkynyl)" are taken to mean a C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety optionally substituted at any available carbon atom in the C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety.

The term "nitrogen protecting group" is taken to mean a moiety that is stable to projected reaction conditions and yet may be selectively removed by reagents and reaction conditions compatible with the regenerated amine. Such groups are well known by the skilled artisan and are described in the literature. (See, for example: Greene and Wuts, Protective Groups in Organic Synthesis, Second Edition, Chapter 7, John Wiley and Sons Inc., (1991)). Nitrogen protecting groups contemplated include:

a) suitable carbamates, such as:

   1) C_1-C_7 alkyl carbamates including methyl, ethyl, tert-butyl, tert-amyl, diisopropylmethyl carbamates, and the like;

   2) substituted ethyl carbamates, such as 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloro-ethyl, 2-(pyridin-2-yl)ethyl, 2-(pyridin-4-yl)ethyl, 2-methylthioethyl, 2-

methylsulfonylethyl, 2-(p-toluenesulfonyl)ethyl, 2-phosphonioethyl, 1,1-dimethyl-2-cyanoethyl, 2-iodoethyl carbamates, and the like;

3) 1-adamantyl carbamate;

4) vinyl carbamate;

5) allyl carbamate;

6) 1-isopropylallyl carbamate;

7) cinnamyl carbamates, such as cinnamyl carbamate, 4-nitrocinnamyl, and the like;

8) 8-quinolinyl carbamate;

9) N-hydroxypiperidinyl carbamate;

10) C_1-C_4 alkyldithio carbamates;

11) Benzyl carbamates, such as benzyl, 4-methoxybenzyl, 4-nitrobenzyl, 4-halobenzyl, 4-cyanobenzyl, 4-decyloxybenzyl, 2,4-dichlorobenzyl, 3,5-dimethoxybenzyl, 2-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl (2-nitrophenyl)methyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl, 3-chloro-4-(C_2-C_6 acyloxy)benzyl, 4-(dihydroxyboryl)benzyl carbamates, and the like;

12) 2-(1,3-dithianyl)methyl carbamate;

13) aryl carbamates, such as phenyl, nicotinyl, 4-(methylthio)phenyl, 2,4-di(methylthio)phenyl, 3-nitrophenyl carbamates, and the like;

14) 2-triphenylphosphonioisopropyl carbamate;

15) 5-benzisoxazolylmethyl carbamate;

16) 2-(trifluoromethyl)-6-chromonylmethyl carbamate;

17) S-benzyl thiocarbamate; and

18) C_3-C_7 cycloalkyl carbamates, such as cyclobutyl, cyclopentyl, 1-methylcyclohexyl, cyclopropylmethyl carbamates, and the like;

b) suitable ureas, such as:

1) phenothiazinyl-(10)-carbonyl;

2) N'-(p-toluenesulfonylaminocarbonyl); and

3) N'-phenylaminothiocarbonyl;

c) suitable formyl and acyl groups, such as:

1) formyl; and

2) acetyl groups, such as acetyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, 4-chlorobutanoyl, phenylacetyl, 3-phenylpropanoyl, N-benzoylphenylalanyl, 2-nitrophenylacetyl, 2-nitrophenoxyacetyl, acetoacetyl, and the like;

d) suitable aroyl groups, such as:

1) picolinoyl;

2) 3-pyridinylcarbonyl;

3) benzoyl;

4) 4-phenylbenzoyl;

5) 2-nitrobenzoyl; and

6) 2-nitrocinnamoyl, and the like;

e) suitable cyclic imide groups, such as:

1) N-phthalimide;

2) N-dithiasuccinimide;

3) N-2,3-diphenylmaleimide; and

4) N-2,5-dimethylpyrrole, and the like;

f) allyl;

g) 3-acetoxypropyl;

h) suitable benzylic groups, such as benzyl, 2-methylbenzyl, α-methylbenzyl, and the like;

i) triphenylmethyl; and

j) suitable imine moieties, such as:

1) 1,1-dimethylthiomethyleneimine;

2) benzylidene imine; and

3) diphenylmethyleneimine, and the like.

The term "inhibition of production of A-β peptide" is taken to mean decreasing of excessive in vivo levels of A-β peptide in a mammal to normal or sub-normal levels.

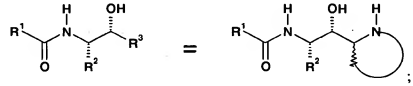
The term "effective amount of a compound of Formula I" is taken to mean the dose or doses of a compound of Formula I required to inhibit BACE sufficiently to decrease in vivo levels of A-β peptide in a mammal to normal or sub-normal levels.

The term "treatment" includes treating one or more disease symptoms present in a patient as well as slowing, arresting, or reversing the progression of the disease.

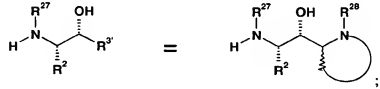
The term "BACE" includes both BACE1 and BACE2.

Mild cognitive impairment has been defined as a potential prodromal phase of dementia associated with Alzheimer's disease based on clinical presentation and on progression of patients exhibiting mild cognitive impairment to Alzheimer's dementia over time. (Morris, et al., Arch. Neurol., **58**, 397-405 (2001); Petersen, et al., Arch. Neurol., **56**, 303-308 (1999)). The term "prevention of the progression of mild cognitive impairment to Alzheimer's disease" includes slowing, arresting, or reversing the progression of mild cognitive impairment to Alzheimer's disease in a patient.

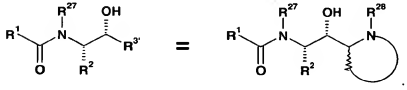
Variable R^3 and $R^{3'}$ represent a variety of cyclic amines in Formulae I, II and III. For the sake of clarity and convenience, the following generic representations will be used interchangeably to represent the compounds of Formula I, Formula II, and Formula III, respectively:



Equivalent Representations of Formula I

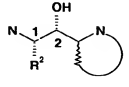


Equivalent Representations of Formula II



Equivalent Representations of Formula III

The skilled artisan will appreciate that compounds of Formulae I, II, and III are comprised of a 1-amino-2-hydroxyethyl core that contains two chiral centers:



Although the present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates, the 1(S),2(R) diastereomer is preferred for compounds of Formula I. The preferred diastereomers of compounds of Formulae II and III are those that will result in the 1(S),2(R) diastereomer when the intermediate is converted to a compound of Formula I. The skilled artisan will also appreciate that the cyclic amine moiety corresponding to variables R^3 and $R^{3'}$ in these formulae introduces a third chiral center into the molecules. Although the present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates, it is preferred that compounds of the invention exist as single enantiomers at the chiral center introduced by the moieties R^3 and $R^{3'}$. Additionally, the skilled artisan will appreciate that additional chiral centers may be created in the compounds of the invention by the selection of certain variables. The present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates. The single enantiomers or diastereomers may be prepared beginning with chiral reagents or by stereoselective or stereospecific synthetic techniques. Alternatively, the single enantiomers or diastereomers may be isolated from mixtures by standard chiral chromatographic or crystallization techniques at any convenient point in the synthesis of compounds of the invention. Single enantiomers and diastereomers of compounds of the invention are a preferred embodiment of the invention.

It will be understood by the skilled reader that most or all of the compounds of Formula I, II, and III are capable of forming salts. In all cases, the pharmaceutically acceptable salts of all of the compounds are included in the names of them. The compounds of the present invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid and trifluoroacetic acid.

Although all of the compounds of Formula I are useful inhibitors of BACE, certain classes of compounds are preferred. The following paragraphs describe such preferred classes:

a) R^1 is hydrogen;

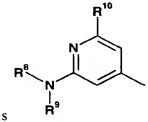
b) R^1 is C_1-C_6 alkyl;

c) R^1 is C_1-C_4 alkyl;

d) R^1 is C_1-C_2 alkyl;

e) R^1 is methyl optionally substituted with chloro or fluoro

f) R^1 is methyl;

g) R^1 is  ;

h) R^2 is benzyl optionally mono- or difluorinated in the phenyl ring;

i) R^2 is benzyl;

j) R^2 is 3-fluorobenzyl;

k) R^2 is 3,5-difluorobenzyl;

l) R^3 is piperidin-2-yl optionally substituted with methyl or ethyl;

m) R^3 is 6-methylpiperidin-2-yl;

n) R^3 is 6-ethylpiperidin-2-yl;

o) R^3 is pyrrolidin-2-yl optionally substituted with one or two fluorine atoms;

p) R^3 is pyrrolidin-2-yl;

q) R^3 is 4-fluoropyrrolidin-2-yl;

r) R^3 is 4,4-difluoropyrrolidin-2-yl;

s) R^3 is 1-(C_1-C_6 alkyl)piperazin-2-on-3-yl;

t) R^3 is 1-methylpiperazin-2-on-3-yl;

u) R^3 is 1,2,3,4-tetrahydroisoquinolin-3-yl optionally substituted with one or two substituents selected from halo and C_1-C_6 alkyl;

v) R^3 is 1,2,3,4-tetrahydroisoquinolin-3-yl;

w) R^8 is hydrogen;

x) R^8 is methyl;

y) R^9 is sec-butyl; and

z) R^{10} is -$NR^{17}SO_2R^{18}$ where R^{17} and R^{18} are both methyl;

aa) The compound of Formula I is a free base;

ab) The compound of Formula I is a pharmaceutically acceptable salt;

ac) The compound of Formula I is the hydrochloride salt.

Preferred embodiments of the invention include all combinations of paragraphs a)-ac). Especially preferred compounds of Formula I are those where R^1 is C_1-C_6 alkyl and R^2 is benzyl, 3-fluorobenzyl, or 3,5-difluorobenzyl. Most preferred compounds of Formula I are those where R^1 is methyl and R^2 is benzyl, 3-fluorobenzyl, or 3,5-difluorobenzyl.

Although all of the compounds of Formula II are useful intermediates for the preparation of BACE inhibitors, certain of the compounds are preferred:

ad) R^2 is benzyl optionally mono- or difluorinated in the phenyl ring;

ae) R^2 is benzyl;

af) R^2 is 3-fluorobenzyl;

ag) R^2 is 3,5-difluorobenzyl;

ah) R^{27} is hydrogen;

ai) R^{27} is a nitrogen protecting group;

aj) R^{27} is benzyl;

ak) R^{27} is 2-methylbenzyl;

al) R^{28} is hydrogen;

am) R^{28} is a carbamate protecting group;

an) R^{28} is tert-butoxycarbonyl;

ao) R^{28} is α-methylbenzyl;

ap) one of R^{27} and R^{28} is hydrogen and the other is a nitrogen protecting group;

aq) R^{27} is hydrogen and R^{28} is tert-butoxycarbonyl or α-methylbenzyl;

ar) R^{27} is hydrogen and R^{28} is tert-butoxycarbonyl;

as) R^{27} is hydrogen and R^{28} is α-methylbenzyl;

at) both R^{27} and R^{28} are independently a nitrogen protecting group;

au) R^{27} is benzyl or 2-methylbenzyl and R^{28} is tert-butoxycarbonyl or α-methylbenzyl;

av) The compound of Formula II is a free base;

aw) The compound of Formula II is a salt.

Preferred embodiments of compounds of Formula II include all combinations of paragraphs ad) – aw). Especially preferred compounds of Formula II are those where both R^{27} is hydrogen and R^{27} is tert-butoxycarbonyl or α-methylbenzyl.

Although all of the compounds of Formula III are useful intermediates for the preparation of BACE inhibitors, certain of the compounds are preferred:

ax) R^1 is hydrogen;

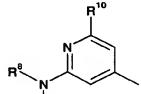
ay) R^1 is C_1-C_6 alkyl;

az) R^1 is C_1-C_4 alkyl;

ba) R^1 is C_1-C_2 alkyl;

bb) R^1 is methyl optionally substituted with chloro or fluoro

bc) R^1 is methyl;

bd) R^1 is  ;

be) R^2 is benzyl optionally mono- or difluorinated in the phenyl ring;

bf) R^2 is benzyl;

bg) R^2 is 3-fluorobenzyl;

bh) R^2 is 3,5-difluorobenzyl;

bi) R^8 is hydrogen;

bj) R^8 is methyl;

bk) R^9 is sec-butyl; and

bl) R^{10} is $-NR^{17}SO_2R^{18}$ where R^{17} and R^{18} are both methyl;

bm) R^{27} is hydrogen;

bn) R^{27} is a nitrogen protecting group;

bo) R^{27} is benzyl;

bp) R^{27} is 2-methylbenzyl;

bq) R^{28} is a carbamate protecting group;

br) R^{28} is tert-butoxycarbonyl;

bs) R^{28} is benzyl;

bt) R^{28} is α-methylbenzyl;

bu) The compound of Formula III is a free base;

bv) The compound of Formula III is a salt.

Preferred embodiments of compounds of Formula III include all combinations of paragraphs ax) – bv). Especially preferred compounds of Formula III are those where R^1 is C_1-C_6 alkyl, R^2 is benzyl, 3-fluorobenzyl, or 3,5-difluorobenzyl, R^{27} is hydrogen and R^{28} is tert-butoxycarbonyl or α-methylbenzyl. Most preferred compounds of Formula III are those where R^1 is methyl, R^2 is benzyl, 3-fluorobenzyl, or 3,5-difluorobenzyl, R^{27} is hydrogen and R^{28} is tert-butoxycarbonyl or α-methylbenzyl.

The compounds of Formula I are inhibitors of BACE. It is preferred the compound of Formula I selectively inhibits BACE1 relative to BACE2. Thus, the present invention also provides a method of inhibiting BACE in a mammal that comprises administering to a mammal in need of said treatment a BACE-inhibiting amount of a compound of Formula I. It is preferred that the mammal to be treated by the administration of the compounds of Formula I is human.

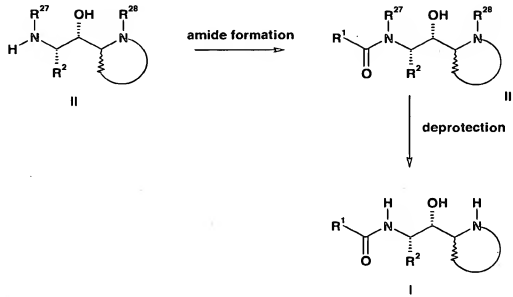
As inhibitors of BACE, the compounds of the present invention are useful for suppressing the production of A-β peptide, and therefore for the treatment of disorders resulting from excessive A-β peptide levels due to over-production and or reduced clearance of A-β peptide. The compounds of Formula I are therefore believed to be useful in treating or preventing Alzheimer's disease, mild cognitive impairment, Down's Syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias such as: dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the present invention may be prepared by a variety of procedures, some of which are illustrated in the Schemes below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to provide the compounds of Formula I. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties. Some substituents have been eliminated in the following schemes for the sake of clarity

and are not intended to limit the teaching of the schemes in any way. Furthermore, individual isomers, enantiomers, or diastereomers may be separated at any convenient point in the synthesis of compounds of Formula I.

The compounds of Formula I may be prepared as described in Scheme I where variables R^1, R^2, R^{27}, and R^{28} are as previously defined:

Scheme I



II III I

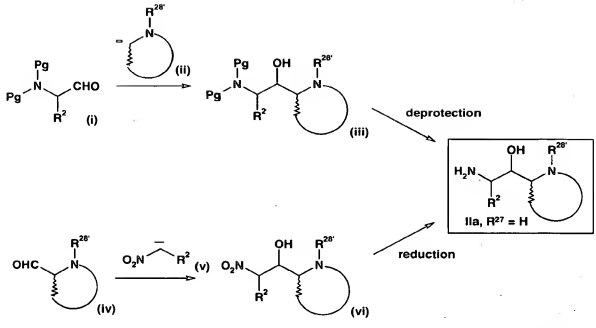
The amine of Formula II is reacted under standard amide forming conditions well known to the skilled artisan to provide compounds of Formula III (for example, see WO 03/040096 and WO 04/024081). An appropriate carboxylic acid of Formula R^1-COOH or an equivalent thereof, such as the sodium or, preferably, potassium carboxylate salt is reacted with a peptide coupling agent such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), or n-propylphosphonic anhydride, and an appropriate amine such as N-methylmorpholine or triethylamine, in a suitable solvent such as dichloromethane, dimethylformamide (DMF) or tetrahydrofuran (THF) to provide the compound of Formula III. If necessary or required, an additive such as 4-(dimethylamino)pyridine and/or 1-hydroxybenzotriazole or equivalents thereof may be added to the reaction mixture to facilitate the reaction. Alternatively, other carboxylic acid equivalents, including acylating agents, such as an appropriate acylimidazole, or a mixed anhydride, such as formic acetic anhyride, or an appropriate acid halide may be reacted directly with the amine of Formula II to provide

the desired amide. The requisite carboxylic acids, carboxylic acid salts, acylating agents, and mixed anhydrides are either commercially available or may be prepared from commercially available materials by methods well known to the skilled artisan. (For example, See: Comprehensive Organic Transformations, Larock, VCH Publishers, Inc., New York, (1989); Advanced Organic Chemistry, March, Wiley Interscience, New York, Third Edition, (1985))

The conditions for deprotection of Formula III to provide compounds of Formula I depend on the nature of variables R^{27} and R^{28}. The deprotection conditions are those well known to the skilled artisan and are described in the literature. (For example, see: Greene and Wuts, Protective Groups in Organic Synthesis, Second Edition, Chapter 7, John Wiley and Sons Inc., (1991)). Again, depending upon the nature of variables R^{27} and R^{28}, they may both be removed in a single reaction, for example by treatment with acid or under hydrogenation conditions, or may be removed sequentially as necessary or desired. The skilled artisan will appreciate that where both R^{27} and R^{28} are hydrogen, no deprotection step is necessary. Further, if salts of compounds of the invention are desired, an appropriate free base of Formula I is simply reacted with an appropriate pharmaceutically acceptable acid in a suitable solvent under standard conditions to provide a pharmaceutically acceptable salt of a compound of Formula I. The skilled artisan will appreciate that, depending on the nature of variables R^{27} and R^{28}, the deprotection and salt forming steps may occur simultaneously to provide a pharmaceutically acceptable salt of a compound of Formula I in a single step.

Intermediates of Formula II may be prepared as described in the following scheme where Pg and $R^{28'}$ represent nitrogen protecting groups and R^2 is as previously defined.

Scheme II



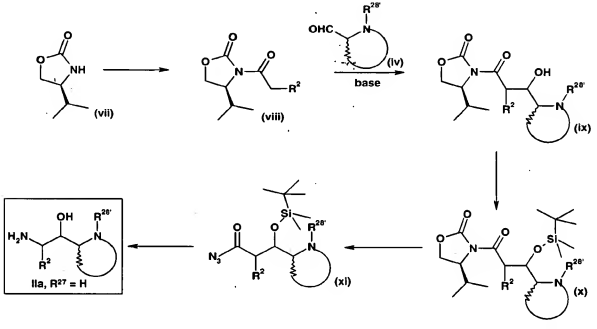
The N,N-diprotected aminoaldehyde (i) is reacted with the anion of appropriately substituted cyclic amine (ii) at low temperature in a suitable solvent, for example tetrahydrofuran, to provide the N,N-diprotected aminoethanol (iii). The amine moiety is deprotected under standard conditions (For example, see: Greene and Wuts, Protective Groups in Organic Synthesis, Second Edition, Chapter 7, John Wiley and Sons Inc., (1991)) to provide the desired aminoethanol. Alternatively, aldehyde (iv) is reacted with the anion of an appropriately substituted nitroalkane (v) to provide the corresponding nitroethane (vi). The nitroethane is reduced to provide the desired aminoethanol. The requisite anions are prepared by treating the appropriately substituted cyclic amine or appropriately substituted nitroethane with a suitable base at low temperature. The requisite appropriately substituted cyclic amines, appropriately substituted nitroethanes, and appropriately substituted aldehydes are either commercially available or may be prepared from commercially available starting materials. (For example, see: Comprehensive Organic Transformations, Larock, VCH Publishers, Inc., New York, (1989); Advanced Organic Chemistry, March, Wiley Interscience, New York, Third Edition, (1985))

A further alternative to Scheme II is to react the anion of an appropriately substituted pyrrole or pyridine with a N,N-diprotected aminoaldehyde (i). The pyrrole or

pyridine moiety in the resulting N,N-diprotected aminoethanol must then be hydrogenated in an additional step to provide the desired aminoethanols (iii).

The compounds of Formula II may also be prepared as described in Scheme III where variable R^2 and $R^{28'}$ are as previously defined.

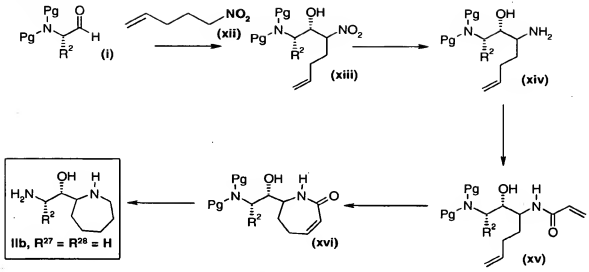
Scheme III



4-(S)-Isopropyloxazolidin-2-one (vii) is deprotonated with a suitable base, such as n-butyllithium in tetrahydrofuran, and then acylated with an appropriately substituted carboxylic acid derivative, such as an acid halide or acid anhydride, to provide the substituted acetamide (viii). This acetamide is deprotonated by reaction with a suitable base, such as N,N-diisopropylethylamine and reacted with aldehyde (iv) to provide the corresponding alcohol (ix). This alcohol is protected with an oxygen protecting group, preferably tert-butyldimethylsilyl, to provide the oxazolidin-2-one intermediate (x). This intermediate is then reacted with basic hydrogen peroxide followed by treatment with a source of azide, such as diphenylphosphoryl azide, to provide the azidocarbonyl intermediate(xi). Treatment of the azidocarbonyl with benzyl alcohol followed by catalytic hydrogenation provides the desired amine (IIa).

Intermediates of Formula IIa where the cyclic amine moiety is a homopiperidine may be prepared as described in Scheme IV where Pg and R^2 are as previously defined.

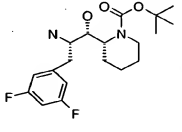
Scheme IV



The anion of nitroalkene (xii) is reacted with diprotected aminoaldehyde (i) in a suitable solvent such as tetrahydrofuran to provide the nitroalcohol (xiii). This nitroalcohol is reduced to the corresponding aminoalcohol (xiv), which is then acylated with acryloyl chloride to provide the corresponding amide (xv). This amide is reacted with Grubb's catalyst to provide the 1,5,6,7-tetrahydroazepin-2-one (xvi). The carbonyl and double bond of this lactam are reduced by treatment with borane-dimethyl sulfide complex. The terminal amine is then deprotected to provide the aminoalcohol (IIb).

Preparation 1

2-(R)-[2-(S)-Amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester



[2-(3,5-Difluorophenyl)-1-(S)-hydroxymethyl-ethyl]-carbamic acid tert-butyl ester

Dissolve commercially available 2-(S)-tert-butoxycarbonylamino-3-(3,5-difluorophenyl)propionic acid (5.995 g, 19.9 mmol) in ethylene glycol dimethyl ether (20 mL) and cool –20 °C. Add 4-methylmorpholine (2.4 mL, 21.89 mmol) and stir 5 min, then add isobutyl chloroformate (2.9 mL, 21.89 mmol) dropwise and stir 5 min. Filter into –15°C cooled flask with course frit, rinse with cold ethylene glycol dimethyl ether. Add sodium borohydride (1.129 g, 29.85 mmol) in water (9 mL) followed by water (500 mL), then warm to RT. Filter and dissolve solid in dichloromethane. Wash with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a solid (4.57 g, 80%).

MS (ES): m/z = 188.0 [M+H, prod-Boc].

2-(S)-Amino-3-(3,5-difluorophenyl)-propan-1-ol trifluoroacetate

Dissolve [2-(3,5-difluorophenyl)-1-(S)-hydroxymethyl-ethyl]-carbamic acid tert-butyl ester (4.57 g, 15.9 mmol) in dichloromethane (20 mL). Add trifluoroacetic acid (20 mL) and stir 45 min and concentrate to give the title compound as a thick residue.

MS (ES): m/z = 352.8 [M+H].

2-(S)-[Bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-propan-1-ol

Dissolve 2-(S)-amino-3-(3,5-difluorophenyl)-propan-1-ol trifluoroacetate (5.61 g, 15.9 mmol) in 10% aqueous ethanol (80 mL). Add potassium carbonate (8.79 g, 64 mmol) and 2-methylbenzyl bromide (4.7 mL, 35.0 mmol) and stir for 2 h. Dilute with dichloromethane (100 mL) and filter. Concentrate filtrate and partition in dichloromethane and water. Extract aqueous twice with dichloromethane, combine organics and wash with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate. Purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a thick residue (4.30 g, 68%).

MS (ES): m/z = 396.2 [M+H].

2-(S)-[Bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-propionaldehyde

Dissolve 2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-propan-1-ol (1.34 g, 3.38 mmol) in DMSO (3 mL) and cool in an ice bath. Add triethylamine (1.9 mL, 13.51 mmol) followed by sulfur trioxide-pyridine complex (1.07 g, 6.76 mmol). Stir 30 min then slowly add water (1.5 mL). Dilute with ethyl acetate and wash with 5% aqueous citric acid (3x), saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a light yellow residue.
MS (ES): m/z = 394.2 [M+H].

2-(S)-[Bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-pyridin-2-yl-propan-1-(S)-ol

Dissolve 2-bromopyridine (0.485 mL, 5.07 mmol) in THF (30 mL) and cool to −78°C. Add n-butyllithium (2.0 mL, 2.5 M in hexanes). Slowly add 2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-propionaldehyde (1.37 g, 3.3 mmol) in THF (10 mL) and stir 2 h. Quench reaction with saturated aqueous ammonium chloride. Warm to RT. Wash organic layer twice with 5% aqueous citric acid, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify twice (silica gel chromatography, eluting with hexanes and ethyl acetate, and then dichloromethane and ethyl acetate) to give the title compound as a foam (0.636 g, 40%).
MS (ES): m/z = 473.2 [M+H].

2-(S)-[Bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S/R)-piperidin-2-yl-propan-1-(R)-ol

Add 2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-pyridin-2-yl-propan-1-(S)-ol (0.55 g, 1.16 mmol) , 5% platinum on carbon sulfided (215 mg), glacial acetic acid (1 mL) and methanol (25 mL) and stir under 1 atmosphere of hydrogen gas. Add filter agent, filter and concentrate. Add dichloromethane and wash with saturated aqueous sodium bicarbonate, dry (magnesium sulfate) and concentrate to give the title compound as a white foam (0.435 g, 78%).
MS (ES): m/z = 479.3 [M+H].

2-(S)-[2-(S)-[Bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester and 2-(R)-[2-(S)-[Bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester

Add di-tert-butyl dicarbonate (1.94 g, 8.9 mmol) to a solution of 2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S/R)-piperidin-2-yl-propan-1-(R)-ol (0.425 g, 0.89 mmol) and triethylamine (0.43 mL, 3.1 mmol) in dichloromethane (20 mL). Stir 18 h at RT and wash with water (2 x 50 mL), saturated aqueous sodium chloride, dry (magnesium sulfate) and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compounds as a foam (0.042 g, 8%) of 2-(S)-[2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester and (0.33 g, 64%) of 2-(R)-[2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester.

MS (ES): m/z = 579.3 [M+H].

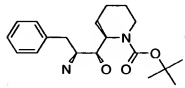
2-(R)-[2-(S)-Amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester

Add 2-(R)-[2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester (0.33 g, 0.56 mmol), 20% palladium hydroxide on carbon (230 mg) and methanol (25 mL) and stir under 1 atmosphere of hydrogen gas for 18 h. Add filter agent, filter and concentrate to give the title compound as a foam (0.203 g, 98%).

MS (ES): m/z = 371.2 [M+H].

Preparation 2

2-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-piperidine-1-carboxylic acid tert-butyl ester



2-(S)-Dibenzylamino-3-phenylpropionaldehyde

Dissolve 2-(S)-dibenzylamino-3-phenylpropan-1-ol (5.00 g, 15.08 mmol) in DMSO (15 mL) and cool in an ice bath. Add triethylamine (8.4 mL, 60.0 mmol) followed by sulfur trioxide-pyridine complex (4.80 g, 30.2 mmol), stir 30 min then slowly add water (15 mL). Dilute with ethyl acetate and wash with 5% aqueous citric acid (3x), saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a light yellow residue.

MS (ES): m/z = 330.2 [M+H].

2-(S)-Dibenzylamino-3-phenyl-1-pyridin-2-yl-propan-1-(S)-ol

Dissolve 2-bromopyridine (2.73 mL, 28.63 mmol) in THF (150 mL) and cool to –78°C. Add n-butyllithium (12.0 mL, 2.5 M in hexanes). Slowly add 2-(S)-dibenzylamino-3-phenyl-propionaldehyde (4.71 g, 14.31 mmol) in THF (15 mL) and stir 30 min. Quench reaction with saturated aqueous ammonium chloride. Remove cold bath and warm to RT. Wash organic layer twice with 5% aqueous citric acid, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with dichloromethane and ethyl acetate) to give the title compound as a residue (3.654 g, 62%).

MS (ES): m/z = 409.3 [M+H].

2-(S)-Dibenzylamino-3-phenyl-1-piperidin-2-(R/S)-yl-propan-1-(R)-ol

Add 2-(S)-dibenzylamino-3-phenyl-1-pyridin-2-yl-propan-1-(S)-ol (1.05 g, 2.57 mmol), 5% platinum on carbon sulfided (215 mg), glacial acetic acid (2 mL) and methanol (40 mL) and stir 18 h under 1 atmosphere of hydrogen gas. Add filter agent, filter and concentrate. Add ethyl acetate and wash with saturated aqueous sodium

bicarbonate, dry (magnesium sulfate) and concentrate to give the title compound as a white foam (1.005 g, 94%).

MS (ES): *m/z* = 415.3 [M+H].

2-(S)-(2-(S)-Dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-piperidine-1-carboxylic acid tert-butyl ester and 2-(R)-(2-(S)-Dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-piperidine-1-carboxylic acid tert-butyl ester

Add di-tert-butyl dicarbonate (4.7 g, 21.6 mmol) to a solution of 2-(S)-dibenzylamino-3-phenyl-1-piperidin-2-(R/S)-yl-propan-1-(R)-ol (0.895 g, 2.16 mmol) and triethylamine (1.05 mL, 7.55 mmol) in dichloromethane (20 mL). Stir 18 h at RT and wash with water (2 x 50 mL), saturated aqueous sodium chloride, dry (magnesium sulfate) and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compounds as a foam, 2-(S)-(2-(S)-dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-piperidine-1-carboxylic acid tert-butyl ester (0.077 g, 7%) and 2-(R)-(2-(S)-dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-piperidine-1-carboxylic acid tert-butyl ester (0.521 g, 47%).

MS (ES): *m/z* = 515.3 [M+H].

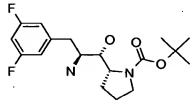
2-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-piperidine-1-carboxylic acid tert-butyl ester

Add 2-(R)-(2-(S)-dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-piperidine-1-carboxylic acid tert-butyl ester (0.107 g, 0.21 mmol), 20% palladium hydroxide on carbon (60 mg) and methanol (5 mL) and stir 18 h under 1 atmosphere of hydrogen gas. Add filter agent, filter and concentrate to give the title compound as a foam.

MS (ES): *m/z* = 335.2 [M+H].

Preparation 3

2-(R)-[2-(S)-Amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-pyrrolidine-1-carboxylic acid tert-butyl ester



2-[2-(S)-[Bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-pyrrole-1-carboxylic acid tert-butyl ester

Add n-butyllithium (3.30 mL, 8.25 mmol, 2.5 M in hexanes) to a solution of 2,2,6,6-tetramethylpiperidine (1.40 mL, 8.18 mmol) in THF (30 mL) at –78°C over 2 min. Stir 5 min, then warm to –10°C and stir 5 min, then cool to –78°C. Add N-tert-butoxycarbonylpyrrole (1.37 mL, 8.25 mmol) in THF (1.6 mL) over 3 min. Stir 30 min and add 2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-propionaldehyde (2.96 g, 7.44 mmol) in THF (15 mL) over 5 min. Stir 60 min at –78°C, warm to 0°C and stir 60 min. Cool –78°C and quench with saturated aqueous ammonium chloride solution. Extract with ethyl acetate, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with hexanes and dichloromethane) to give the title compound as a foam (0.416 g, 10%).

MS (ES): *m/z* = 561.2 [M+H].

2-(R)-[2-(S)-[Bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

Add 2-[2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-pyrrole-1-carboxylic acid tert-butyl ester (0.415 g, 0.74 mmol), 10% platinum on carbon (0.087 g) and methanol (15 mL) and hydrogenate at one atmosphere hydrogen gas for 18 h. Add filter agent and filter, concentrate and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a white foam (0.116 g, 28%).

MS (ES): *m/z* = 564.3 [M+H].

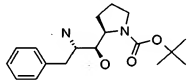
2-(R)-[2-(S)-Amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

Add 2-(R)-[2-(S)-[bis-(2-methylbenzyl)-amino]-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.116 g, 0.205 mmol), 20% palladium on carbon (0.069 g) and methanol (3 mL) and hydrogenate at one atmosphere hydrogen gas for 18 h. Add filter agent and filter and concentrate to give the title compound as a residue (0.069 g, 94%).

MS (ES): *m/z* = 357.3 [M+H].

Preparation 4

2-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



2-(S)-Dibenzylamino-3-phenyl-propionaldehyde

Dissolve 2-(S)-dibenzylamino-3-phenylpropan-1-ol (5.00 g, 15.08 mmol) in DMSO (15 mL) and cool in an ice bath. Add triethylamine (8.4 mL, 60.0 mmol) followed by sulfur trioxide-pyridine complex (4.80 g, 30.2 mmol). Stir 30 min then slowly add water (15 mL). Dilute with ethyl acetate and wash with 5% aqueous citric acid (3x), saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a light yellow residue.

MS (ES): *m/z* = 330.2 [M+H].

2-(R)-(2-(S)-Dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Add sec-butyllithium (1.29 mL, 1.8 mmol) dropwise to a solution of (-)-sparteine (0.44 mL, 1.36 mmol) in diethyl ether (10 mL) over 3 min at –78°C. Add N-Boc-pyrrolidine (0.245 mL, 1.4 mmol) in diethyl ether (2 mL) dropwise over 10 min. Stir 2 h, add 2-(S)-dibenzylamino-3-phenylpropionaldehyde (0.69 g, 2.1 mmol) in diethyl ether (1.8 mL) over 5 min and stir 20 min. Add acetic acid (0.16 mL) and warm to RT. Add

saturated aqueous sodium chloride (20 mL), separate layers, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a foam (0.421 g, 60%).

MS (ES): m/z = 501.3 [M+H].

2-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Dissolve 2-(R)-(2-(S)-dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.49 mmol) in methanol (20 mL). Add 20% palladium hydroxide on carbon (0.33 g) and stir 1 h under one atmosphere of hydrogen gas. Filter through filter agent and concentrate to give the title compound as a white foam (0.45 g, 93%).

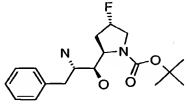
MS (ES): m/z = 321.2 [M+H].

The compound of Preparation 5 may be prepared essentially as described in Preparation 4 except 2-(S)-dibenzylaminopropan-1-ol is used.

Prep	Compound	MS [M+H]
5	2-(R)-[(2-(S)-Amino-1-(S)-hydroxypropyl)]-pyrrolidine-1-carboxylic acid tert-butyl ester	321.2

Preparation 6

2-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-4-(S)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester



4-(R)-Hydroxypyrrolidine-2-(R)-carboxylic acid methyl ester hydrochloride

Add thionyl chloride (5.5 mL, 75.8 mmol) to an ice-cold suspension of 4-(R)-hydroxypyrrolidine-2-(R)-carboxylic acid (4.97 g, 31.9 mmol) in methanol (60 mL). Stir 10 min, then warm to RT and stir 3.5 h. Concentrate, add methanol, and concentrate again. Dissolve in absolute ethanol (25 mL) and precipitate with diethyl ether (50 mL)

and filter. Dry cake under vacuum to give the title compound as a white solid (4.77 g, 82%).

MS (ES): m/z = 146.1 [M+H].

4-(R)-Hydroxypyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

Add di-tert-butyl dicarbonate (10.4 g, 47.7 mmol) in 1,4-dioxane (10 mL) to a solution of 4-(R)-hydroxypyrrolidine-2-(R)-carboxylic acid methyl ester hydrochloride (6.66 g, 36.7 mmol) in 1,4-dioxane (80 mL). Cool in an ice bath and add N,N-diisopropylethylamine (11 mL, 62.4 mmol), then remove ice bath and stir 1 h at RT. Concentrate and dissolve in ethyl acetate and wash with aqueous citric acid solution (2 x 100 mL), water, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate to give the title compound as a white solid (7.1 g, 79%).

MS (ES): m/z = 246.1 [M+H].

4-(S)-Fluoropyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

Add (diethylamino)sulfur trifluoride (3.9 mL, 29.8 mmol) to a –78 °C cooled solution of 4-(R)-hydroxypyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (3.81 g, 15.54 mmol) in dichloromethane (50 mL). Stir 2 h, then remove cold bath and stir 40 h at RT. Cool in ice bath and add saturated sodium bicarbonate solution. Warm to RT, dry (magnesium sulfate), concentrate (350 mbar, 25°C) and purify (silica gel chromatography, eluting with diethyl ether and dichloromethane) to give the title compound as an oil (4.01 g, 97%).

MS (ES): m/z = 148.1 [M+H, Product-Boc].

4-(S)-Fluoro-2-(R)-hydroxymethylpyrrolidine-1-carboxylic acid tert-butyl ester

Add lithium borohydride (0.43 g, 19.6 mmol) to an ice cold solution of 4-(S)-fluoropyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (3.9 g, 13.08 mmol) in THF (50 mL). Warm to RT over 18 h. Cool in ice bath. Slowly add acetic acid (3 mL) and water and extract with ethyl acetate. Wash extract with water, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a thick oil (2.90 g, 100%).

MS (ES): *m/z* = 218.2 [M+H].

4-(S)-Fluoro-2(R)-formylpyrrolidine-1-carboxylic acid tert-butyl ester

Add triethylamine (1.1 mL, 7.79 mmol) and sulfurtrioxide-pyridine complex (0.63 g, 3.89 mmol) to an ice-cold solution of 4-(S)-fluoro-2-(R)-hydroxymethylpyrrolidine-1-carboxylic acid tert-butyl ester (0.426 g, 1.95 mmol) in DMSO (2 mL). Stir 30 min, warm to RT and stir 30 min. Dilute with diethyl ether and wash with 5% aqueous citric acid (3 x 120 mL), saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as an oil that was used in the next step without further purification.

4-(S)-Fluoro-2-(R)-(1-(S)-hydroxy-2-(S)-nitro-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and 4-(S)-Fluoro-2-(R)-(1-(R)-hydroxy-2-(S)-nitro-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Add tetrabutylammonium fluoride (2.0 mL of 1.0 M solution in THF) to an ice-cold solution of 1-phenyl-2-nitroethane (0.51 mL, 3.79 mmol) in THF (2 mL). Stir 5 min and add 4-(S)-fluoro-2(R)-formylpyrrolidine-1-carboxylic acid tert-butyl ester (0.58 g, 1.95 mmol) in THF (6 mL). Stir 90 min, dilute with ethyl acetate, wash with water (3 x 50 mL), saturated aqueous sodium chloride, dry (magnesium sulfate) and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compounds as foams, 4-(S)-fluoro-2-(R)-(1-(S)-hydroxy-2-(S)-nitro-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.21 g, 29%) and 4-(S)-fluoro-2-(R)-(1-(R)-hydroxy-2-(S)-nitro-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.33 g, 46%). MS (ES): *m/z* = 367.3 [M-H].

2-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-4-(S)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester

Dissolve nickel chloride hexahydrate (0.021 g, 0.09 mmol) and 4-(S)-fluoro-2-(R)-(1-(R)-hydroxy-2-(S)-nitro-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.33 g, 0.897 mmol) in methanol (5 mL). Cool in an ice bath and add sodium borohydride (0.17 g, 4.485 mmol) portionwise over 1 min. Stir 10 min, then concentrate. Partition in water and ethyl acetate and filter through filter agent. Separate layers and wash organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate), and concentrate to give the title compound as a white foam.

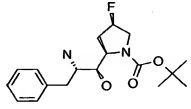
MS (ES): m/z = 339.2 [M+H].

The compound of Preparation 7 may be prepared essentially as described in Preparation 6 except 4-(R)-hydroxypyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester is oxidized to the ketone and then converted to the geminal difluoride. Preparation 8 may be prepared essentially as described in Preparation 6 using nitroethane. Preparation 9 may be prepared essentially as described in Preparation 6 using 1-phenyl-2-nitromethane and 3-(R)-formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (prepared essentially as described in WO 02/059117).

Prep	Compound	MS [M+H]
7	2-(R)-[(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)]-4,4-difluoropyrrolidine-1-carboxylic acid tert-butyl ester	357.2
8	2-(R)-[(2-(S)-Amino-1-(S)-hydroxypentyl)]-pyrrolidine-1-carboxylic acid tert-butyl ester	
9	3-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester	383.3

Preparation 10

2-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-4-(R)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester



4-(S)-Isopropyl-3-(3-phenylpropionyl)-oxazolidin-2-one

Add n-butyllithium (2.5 M solution in hexanes, 32 mL of, 80 mmol) to a solution of 4-(S)-isopropyloxazolidin-2-one (10.26 g, 79.4 mmol) in THF (250 mL) at –78 °C. Stir 30 min. Add 3-phenylpropionyl chloride (13.2 mL, 89 mmol) over 4 min. Stir 2.5 h at –78 °C, then warm to –55 °C and stir 2 h. Add saturated aqueous ammonium chloride (75 mL) and warm to RT. Extract with dichloromethane and wash extract with 1 N NaOH (200 mL), saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate. Add hexanes (50 mL), filter solids and dry under vacuum to give a white solid (18.94 g, 91%).

4-(S)-Hydroxypyrrolidine-2-(R)-carboxylic acid methyl ester

Add thionyl chloride (5.8 mL, 79.4 mmol) to an ice-cold suspension of 4-(S)-hydroxypyrrolidine-2-(R)-carboxylic acid (4.97 g, 31.9 mmol) in methanol (70 mL). Stir 10 min, then warm to RT and stir 3.5 h. Concentrate, add methanol and concentrate again to give the title compound as a white solid (7.18 g, 99%).

MS (ES): m/z = 146.1 [M+H].

4-(S)-Hydroxypyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

Add di-tert-butyl dicarbonate (11.2 g, 51.35 mmol) to a solution of 4-(S)-hydroxypyrrolidine-2-(R)-carboxylic acid methyl ester hydrochloride (7.17 g, 39.5 mmol) in 1,4-dioxane (80 mL). Cool in an ice bath and add N,N-diisopropylethylamine (11.7 mL, 67.2 mmol). Remove ice bath and stir 1 h at RT. Concentrate and dissolve in ethyl acetate, wash with 5% aqueous citric acid solution (2 x100 mL), water, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate),

concentrate and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a white solid (9.83 g, 100%).
MS (ES): m/z = 246.1 [M+H].

4-(R)-Fluoropyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

Add (diethylamino)sulfur trifluoride (10.5 mL, 80 mmol) to a –78 °C cooled solution of 4-(S)-hydroxypyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (9.83 g, 40 mmol) in dichloromethane (60 mL). Stir 2 h, then remove cooling bath and stir 18 h at RT. Heat to reflux for 30 min, then cool in ice bath and add saturated aqueous sodium bicarbonate solution. Warm to RT, dry (magnesium sulfate), concentrate (350 mbar, 25 °C) and purify (silica gel chromatography, eluting with diethyl ether and dichloromethane) and then concentrate at 120 mbar at 25 °C to give the title compound as an oil (9.09 g, 92%).
MS (ES): m/z = 148.1 [M+H, Product-Boc]

4-(R)-Fluoro-2-(R)-hydroxymethylpyrrolidine-1-carboxylic acid tert-butyl ester

Add lithium borohydride (1.03 g, 47.4 mmol) to an ice cold solution of 4-(R)-fluoropyrrolidine-N1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (7.8 g, 31.5 mmol) in THF (100 mL). Let warm to RT over 18 h. Cool in ice bath. Slowly add acetic acid (5 mL) and water and extract with ethyl acetate. Wash extract with water, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a thick oil (5.56 g, 80%).
MS (ES): m/z = 218.2 [M-H].

4-(R)-Fluoro-2-(R)-formylpyrrolidine-1-carboxylic acid tert-butyl ester

Add triethylamine (6.6 mL, 47.7 mmol) and sulfurtrioxide-pyridine complex (3.8 g, 23.9 mmol) to an ice cold solution of 4-(R)-fluoro-2-(R)-hydroxymethylpyrrolidine-1-carboxylic acid tert-butyl ester (2.62 g, 11.9 mmol) in DMSO (12 mL). Stir 30 min, then warm to RT and stir 30 min. Dilute with diethyl ether and wash with 5% aqueous citric acid (3 x 120 mL), saturated aqueous sodium chloride, dry (magnesium sulfate) and

concentrate to give the title compound as an oil that is used in the next step without further purification.

2-(R)-[2-(S)-Benzyl-1-(S)-hydroxy-3-(4-(S)-isopropyl-2-oxo-oxazolidin-3-yl)-3-oxopropyl]-4-(R)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester

Add dibutylboron triflate (1 M in dichloromethane, 11.8 mL, 11.8 mmol) to a solution of 4-(S)-isopropyl-3-(3-phenylpropionyl)-oxazolidin-2-one (2.8 g, 10.7 mmol) in dichloromethane (40 mL) at 0 °C. Stir 5 min. Add N,N-diisopropylethylamine (2.25 mL, 12.87 mmol) and stir 90 min. Cool to –78 °C and add 4-(R)-fluoro-2-(R)-formylpyrrolidine-1-carboxylic acid tert-butyl ester (2.53 g, 11.6 mmol) in dichloromethane (15 mL) over 15 min. Stir 90 min and then warm to RT over 18 h. Cool in ice bath and add 0.05 M pH 7 phosphate buffer (15 mL). Extract with dichloromethane and concentrate. Dissolve in methanol (50 mL) and cool in ice bath. Add aqueous hydrogen peroxide (15 mL, 30% solution) and remove ice bath. Stir 5 min and concentrate. Extract with ethyl acetate and wash extract with 1 N HCl, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a foam (2.68 g, 52%).

MS (ES): m/z = 479.1 [M-H].

2-(R)-[2-(S)-Benzyl-1-(S)-(tert-butyl-dimethylsilanyloxy)-3-(4-(S)-isopropyl-2-oxo-oxazolidin-3-yl)-3-oxopropyll-4-(R)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester

Add 2,6-lutidine (5.3 mL, 54 mmol) and tert-butyl-dimethylsilyl-trifluoromethylsulfonate (1.62 mL, 7.08 mL) to a solution of 2-(R)-[2-(S)-benzyl-1-(S)-hydroxy-3-(4-(S)-isopropyl-2-oxo-oxazolidin-3-yl)-3-oxopropyl]-4-(R)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester (2.585 g, 5.4 mmol) in dichloromethane (40 mL) at –78 °C. Stir 3 h, warm to RT, stir 5 min and cool in an ice bath. Add 1 N HCl (100 mL), wash with 1 N HCl (2 x 100 mL), saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrateand purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a white foam (2.779 g, 87%).

MS (ES): m/z = 593.5 [M+H].

2-(R)-[2-(S)-Azidocarbonyl-1-(S)-(tert-butyl-dimethylsilanyloxy)-3-phenylpropyl]-4-(R)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester

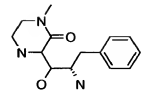
Add an aqueous solution of hydrogen peroxide (30% solution, 2.7 mL, 28.1 mmol) dropwise to a solution of 2-(R)-[2-(S)-benzyl-1-(S)-(tert-butyl-dimethylsilanyloxy)-3-(4-(S)-isopropyl-2-oxo-oxazolidin-3-yl)-3-oxopropyl]-4-(R)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester (2.779 g, 4.69 mmol) in THF (15 mL) at 0 °C. Add 2 N lithium hydroxide (4.7 mL, 9.38 mmol) dropwise, stir 60 min and warm to RT. Add methanol (5 mL) and stir 18 h. Dilute with ethyl acetate and wash with 1 N HCl, saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate. Dissolve residue in dichloromethane (30 mL) and add diisopropylethylamine (1.2 mL, 7.03 mmol) followed by diphenylphosphoryl azide (1.1 mL, 5.16 mmol). Stir 1 h and add diisopropylethylamine (1.2 mL, 7.03 mmol) followed by diphenylphosphoryl azide (1.1 mL, 5.16 mmol). Stir 3.5 h, concentrate and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give the title compound as a residue (0.79 g, 32%).

2-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-4-(R)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester

Heat a solution of benzyl alcohol (1.5 mL, 15 mmol) and 2-(R)-[2-(S)-azidocarbonyl-1-(S)-(tert-butyl-dimethylsilanyloxy)-3-phenylpropyl]-4-(R)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester (0.78 mmol, 1.5 mmol) in toluene (9 mL) to reflux for 18 h. Concentrate and purify (silica gel chromatography, eluting with hexanes and ethyl acetate) to give an oil. Dissolve in methanol (15 mL) and add 10% palladium on carbon (0.1 g) and stir under an atmosphere of hydrogen gas for 1 h. Filter through filter agent, concentrate and purify (silica gel chromatography, eluting with dichloromethane and 2M ammonia in methanol) to give the title compound (0.54 g, 80%). MS (ES): m/z = 453.5 [M+H].

Preparation 11

3-(2-(S)-amino-1-hydroxy-3-phenylpropyl)-1-methylpiperazin-2-one



4-Benzyloxycarbonyl-1-methylpiperazin-2-one

Dissolve 4-benzyloxycarbonylpiperazin-2-one (2 g, 8.6 mmol) in THF (10 mL). Add sodium hydride (236 mg, 9.4 mmol, 60% dispersion in mineral oil) in one portion and stir at RT for 30 min. Add iodomethane (0.8 mL, 13 mmol) and stir at RT overnight. Concentrate, add ethyl acetate and wash with water. Separate organic layer, wash with saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with ethyl acetate) to give the title compound as a yellow oil (1.7g, 82%).

MS (ES): m/z = 249 [M+H].

3-(2-(S)-Dibenzylamino-1-hydroxy-3-phenylpropyl)-4-benzyloxycarbonyl-1-methylpiperazin-2-one

Treat a solution of 4-benzyloxycarbonyl-1-methylpiperazin-2-one (1.4 g, 5.7 mmol) in THF (4 mL) cooled at –78 °C with lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 5.7 mL, 5.7 mmol) dropwise and stir 30 min. Add 2-(dibenzylamino)-3-phenylpropanal (1 g, 3.1 mmol) in THF (2 mL) and stir at –78 °C for 45 min. Quench with saturated aqueous ammonium chloride solution. Separate organic layer and wash with water, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 1:1 hexanes:ethyl acetate) to provide the title compound as a mixture of four diastereoisomers which are separated by HPLC (normal phase, eluting with 85:15 hexanes:isopropanol) (828 mg, 45% total yield).

Isomer-1 (11-A) run time 9.9 min MS (ES): m/z = 578 [M+H].

Isomer-2 (11-B) run time 14.0 min MS (ES): m/z = 578 [M+H].

Isomer-3 (11-C) run time 11.7 min MS (ES): m/z = 578 [M+H].

Isomer-4 (11-D) run time 12.3 min MS (ES): m/z = 578 [M+H].

3-(2-(S)-Amino-1-hydroxy-3-phenylpropyl)-1-methylpiperazin-2-one

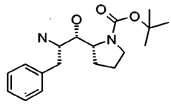
Treat a solution of 3-(2(S)-dibenzylamino-1-hydroxy-3-phenylpropyl)-4-benzyloxycarbonyl-1-methylpiperazin-2-one (Isomer 11-B) (210 mg, 0.36 mmol) in methanol (10mL) with 20% palladium hydroxide on carbon (48 mg) in one portion and stir the mixture under 1 atmosphere of hydrogen gas for 24 h. Filter through a filtering agent, wash with methanol and concentrate to give the title compound as an oil. MS (ES): $m/z = 264$ [M+H].

The compounds of Preparation 12-14 may be prepared essentially as described in Preparation 11.

Prep	Compound	MS [M+H]
12	3-(2(S)-amino-1-hydroxy-3-phenylpropyl)-1-methylpiperazin-2-one, Isomer 1 (From isomer 11-A)	264
13	3-(2(S)-amino-1-hydroxy-3-phenylpropyl)-1-methylpiperazin-2-one, Isomer 3 (From isomer 11-C)	264
14	3-(2(S)-amino-1-hydroxy-3-phenylpropyl)-1-methylpiperazin-2-one Isomer 4 (From isomer 11-D)	264

Preparation 15

2-(R)-(2-(R)-Amino-1-(S)-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



2-(R)-(2-(R)-Dibenzylamino-1-hydroxy-3-phenylpropyl)-pyrrole-1-carboxylic acid tert-butyl ester

Add n-butyllithium (1.6 M in hexanes, 1.06 mL, 1.7 mmol) to a solution of tetramethylpiperidine (0.29 mL, 1.7 mmol) in THF (12 mL) at –78 °C. Stir at –78 °C for 5 min, at –10 °C for 5 min and at –78 °C for 5 min. Add N-Boc-pyrrole and stir the solution for 20 min. Add 2-(S)-dibenzylamino-3-phenylpropionaldehyde dissolved in THF (4 mL) and stir at –78 °C for 45 min. Quench with saturated aqueous ammonium chloride solution and separate the two layers. Extract the aqueous layer with ethyl acetate (2 x 20 mL) and wash the combined organic layers with 1 N HCl, 5% aqueous sodium bicarbonate and saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate

and purify (silica gel chromatography, eluting with 4:1 hexanes:diethyl ether) to give the title compound (240 mg, 32%).

MS (ES): *m/z* = 497 [M+H].

2-(R)-(2-(R)-Dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Dissolve 2-(R)-(2-(R)-dibenzylamino-1-hydroxy-3-phenylpropyl)-pyrrole-1-carboxylic acid tert-butyl ester (160 mg, 0.32 mmol) in methanol (2 mL) and add 10% platinum on carbon (63 mg, 0.032 mmol). Bubble hydrogen gas through the mixture and stir under 1 atmosphere of hydrogen gas overnight. Bubble nitrogen through the mixture for 2 min, filter through a filtering agent, wash with methanol and concentrate. Separate isomers using silica gel chromatography, eluting with 3:1 hexanes:ethyl acetate to give the title compounds as a mixture of 2 isomers, (S) (84 mg, 52%), and isomer (R) (74 mg, 46%).

MS (ES): *m/z* = 501 [M+H].

2-(R)-(2-(R)-Amino-1-(S)-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Dissolve 2-(R)-(2-(R)-dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (610 mg, 1.2 mmol) in methanol (13 mL). Add 20% palladium hydroxide on carbon (157 mg, 0.19 mmol). Bubble hydrogen gas through the mixture and stir under 1 atmosphere of hydrogen gas overnight. Bubble nitrogen through the mixture for 2 min, filter through a filtering agent, wash with methanol and concentrate to give the title compound.

Preparation 16

2-(S)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-3-(S)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester and 2-(S)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-3,3-difluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

3,3-Difluoropyrrolidine-1-carboxylic acid tert-butyl ester

Dissolve 1-N-boc-3-pyrrolidinone (1.70 g, 9.18 mmol) in anhydrous dichloromethane (20 mL) and cool to 0 °C. Add bis (2-methoxyethyl)-aminosulfur trifluoride (5.0 mL, 27.5 mmol) and stir overnight at RT. Pour the solution carefully into saturated aqueous sodium bicarbonate (30 mL) and stir 15min at RT. Collect the organic layer and wash with water (30 mL), saturated aqueous sodium chloride (30 mL), dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 5:95 acetone:hexanes) to give the title compound as a colorless oil (1.33 g, 70%).

5-(2-(S)-Dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-4-fluoro-2,3-dihydropyrrole-1-carboxylic acid tert-butyl ester and 2-(S)-(2-(S)-Dibenzylamino-1-(S)-hydroxy-3-phenyl-propyl)-3,3-difluoropyrrolidine-1-carboxylic acid tert-butyl ester

Dilute (-)-sparteine (2.0 mL, 8.78 mmol) in diethyl ether (10 mL) and cool to –78 °C. Add a solution of sec-butyllithium (1.4 M in cyclohexanes, 6.3 mL, 8.78 mmol,) slowly and stir 10 min. Dilute 3,3-difluoropyrrolidine-1-carboxylic acid tert-butyl ester (0.91 g, 4.39 mmol) in diethyl ether (5 mL) and add dropwise. Stir this solution 3h at –78 °C. Dilute 2-(S)-dibenzylamino-3-phenylpropionaldehyde (2.2 g, 6.59 mmol) in diethyl ether (2 mL) and add slowly. After stirring 45 min quench with of glacial acetic acid (0.2 mL) and allow to warm to RT. Wash the organic layer with saturated aqueous sodium chloride (30 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 15:85 ethyl acetate:hexanes) to give a mixture of the title compounds as a yellow oil (1.44 g, 63%)

MS (ES): m/z = 517.3 [M+H], MS (ES): m/z = 537.3 [M+H].

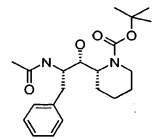
2-(S)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-3-(S)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester and 2-(S)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-3,3-difluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

Add 5-(2-(S)-dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-4-fluoro-2,3-dihydropyrrole-1-carboxylic acid tert-butyl ester and 2-(S)-(2-(S)-dibenzylamino-1-(S)-hydroxy-3-phenylpropyl)-3,3-difluoropyrrolidine-1-carboxylic acid tert-butyl ester (1.43 g, 2.77 mmol), 20% palladium hydroxide on carbon (500 mg) and methanol (15 mL) and stir under 1 atmosphere of hydrogen gas for 18 h. Filter over a pad of filtering agent and concentrate to give a mixture of the title compounds (822 mg, 88%) as an off-white solid. Some dehalogenation is observed.

MS (ES): m/z = 339.2 [M+H], MS (ES): m/z = 357.2 [M+H].

Preparation 17

(R)-2-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester



(R)-2-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester

Add 1-acetylimidazole (0.035 g, 0.315 mmol) and triethylamine (0.04 mL, 0.286 mmol) to solution of 2-(R)-[2-(S)-amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester (0.106 mg, 0.286 mmol) in dichloromethane (10 mL) and stir 18 h at RT. Dilute with ethyl acetate and wash with 1 N hydrochloric acid (3x), saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with dichloromethane and ethyl acetate) to give the title compound as a white solid (0.089 g, 76%).

MS (ES): m/z = 411.2 [M-H].

The compounds of Preparations 18-21 may be prepared essentially as described in Preparation 17 using the appropriate amines.

Prep	Compound	MS [M+H]
18	(R)-2-((1S,2S)-2-Acetylamino-1-hydroxy-3-phenyl-propyl)-piperidine-1-carboxylic acid tert-butyl ester	377.2
19	(R)-2-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-pyrrolidine-1-carboxylic acid tert-butyl ester	397.2
20	(R)-2-((1S,2R)-2-Acetylamino-1-hydroxy-3-phenylpropyl)-4-(S)-(toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester	
21	(R)-2-[(1S,2R)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-4-(S)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester	

Preparation 22

2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid potassium salt

2-(S)-sec-Butylamino-6-chloro-isonicotinic acid methyl ester

Add to a 300 mL autoclave reactor 2,6-dichloroisonicotinic acid methyl ester (20 g, 0.09707 mol), palladium acetate (2.18 g, 0.009707 mol, 0.), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (6.04 g, 0.009707 mol), cesium carbonate (37.95 g, 0.1165 mol) and (S)-(+)-2-sec-butylamine (8.52 g, 0.1165 mol) in toluene (200 mL). Flush with nitrogen 3 times and heat to 90 °C for 23 h. Cool to RT, filter, concentrate the filtrate and purify (silica gel chromatography) to give the title compound as a yellow solid (11.3 g, 48%).

m.p. 62.3-63.0 °C, ^{1}H NMR (500 MHz, DMSO) δ 7.07 (s, 1H), 6.84 (s, 1H), 4.72 (br s, 1H), 3.95 (s, 3H), 3.74 (m, 1H), 1.59 (m, 2H) 1.24 (d, J = 6.5 Hz, 3H), 0.99 (t, J = 7 Hz, 3H).

(S)-(+)-2-sec-Butylamino-6-methanesulfonylamino-isonicotinic acid methyl ester

Add to a 300 mL of autoclave reactor (s)-(+)-2-sec-butylamino-6-chloro-isonicotinic acid methyl ester (12.46 g, 0.05134 mol), bis(dibenzylideneacetone)palladium (0) (2.35 g, 0.002567 mol), 2-di-tert-butylphosphino biphenyl (1.53 g, 0.005134 mol) and sodium methanesulfonamide (12.02 g, 0.1027 mol) in toluene (250 mL). Flush with nitrogen 3 times and heat to 99 °C for 24 h. Filter and

dissolve the filter cake in water (400mL). Extract the aqueous layer with chloroform (3 x 200 mL), dry (magnesium sulfate) and concentrate. Dissolve the crude product in dichloromethane (20 mL) and precipitate out by adding hexanes (400mL) to give a solid (7.18 g, 46%).

m.p. 118.6-123.0 °C, ^{1}H NMR (500 MHz, DMSO) δ 6.87 (s, 1H), 6.69 (s, 1H), 4.83 (br, 1H), 3.94 (s, 3H), 3.74 (m, 1H), 3.27 (s, 1H), 1.60 (m, 2H) 1.25 (d, J = 7 Hz, 3H), 0.99 (t, J = 7 Hz, 3H).

(S)-(+)-2-sec-Butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid methyl ester

Treat a mixture of (s)-(+)-2-sec-butylamino-6-methanesulfonylamino-isonicotinic acid methyl ester (13.63 g, 0.04523 mol) and potassium carbonate (12.50 g, 0.09046 mol) in DMF (42 mL) with iodomethane (7.90 g, 0.05563 mol). Stir at RT for 18 h, and add water (200mL). The aqueous layer was extracted with methyl tert-butyl ether (5 x 150 mL). Wash the combined organic layers with 1 N lithium chloride (5 x 100 mL), dry (magnesium sulfate) and concentrate to give the title compound as a solid (13.19 g, 92%). ^{1}H NMR (500 MHz, DMSO) δ 7.00 (d, J = 7.5 Hz, 1H) 6.84 (s, 1H), 6.77 (s, 1H), 3.85 (s, 3H), 3.80 (m, 1H), 3.26 (s, 3H), 3.21 (s, 3H), 1.54 (m, 2H) 1.13 (m, 3H), 0.99 (t, J = 5.5 Hz, 3H).

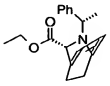
(S)-(+)-2-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinate potassium salt

Heat a mixture of (S)-(+)-2-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid methyl ester (12.66 g, 0.04014 mol) and potassium hydroxide (2.7 g, 0.04817 mol, 1.2 eq) until dissolved. Dilute with water (62 mL) and was heat to reflux for 3 h. Cool to RT and add 1 N HCl (8 mL). Concentrate and add dichloromethane (300 mL) and stir well. Filter and concentrate filtrate to give the title compound as a yellow solid (13.62 g, 100 %).

m.p. 78-83 °C. ^{1}H NMR (500 MHz, DMSO) δ 6.72 (s, 1H), 6.67 (s, 1H), 6.30 (d, J = 7 Hz, 1H) 3.73 (m, 1H), 3.18 (s, 3H), 3.17 (s, 3H), 1.55 (q, 1H) 1.45 (q, 1H), 1.12 (d, J = 5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H).

Preparation 23

2-[1-(S)-Phenylethyl]-2-aza-(1R,4R)-bicyclo[2.2.2]oct-(5Z)ene-3-(R)-carboxylic acid ethyl ester



(S)-(1-phenyl-ethylimino) acetic acid ethyl ester

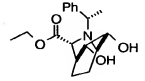
Treat a solution of neat (S)-α-methylbenzylamine (7.5 mL, 59 mmol) in dichloromethane (300 mL) at 0 °C with ethyl glyoxalate solution (50% in toluene, 11.5 mL). Add 4Å molecular sieves (20 g) to the above solution. Stir the reaction mixture at 0 °C for 2 h. Filter the solids off, concentrate and purify (silica gel chromatography, eluting with 20:80 to 70:30 ethyl acetate:hexanes) to give the title compound (11.1 g, 97%)

2-[1-(S)-Phenylethyl]-2-aza-(1R,4R)-bicyclo[2.2.2]oct-(5Z)ene-3-(R)-carboxylic acid ethyl ester and 2-[1-(S)-Phenylethyl-2-aza-(1S,4S)-bicyclo[2.2.2]oct-(5Z)-ene-3-(S)-carboxylic acid ethyl ester

Treat a solution of (S)-(1-phenyl-ethylimino)-acetic acid ethyl ester (2.05 g, 10 mmol) in dichloromethane (50 mL) at –78 °C with trifluoroactetic acid (0.53 mL, 11 mmol), boron trifluoride diethyl etherate (1.39 mL, 11 mmol), followed by 1,3-cyclohexadiene (1.05 mL, 11 mmol). Stir the reaction mixture at –78 °C for 2 h and at –20 °C overnight. Quench the reaction with saturated aqueous sodium bicarbonate. Extract the products with dichloromethane (100 mL). Wash the organic layer with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 10:90 ethyl acetate:hexanes) to give the title compound 2-[1-(S)-phenylethyl]-2-aza-(1R,4R)-bicyclo[2.2.2]oct-(5Z)ene-3-(R)-carboxylic acid ethyl ester (1.22 g, 43%) as Isomer 1, along with the minor product 2-(1-phenylethyl)-2-aza-bicyclo[2.2.2]oct-5-ene-3-carboxylic acid ethyl ester (~10%) as Isomer 2.

Preparation 24

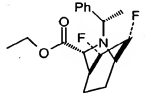
(5R,6S)-Dihydroxy-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester



Treat a solution of 2-[1-(S)-phenylethyl]-2-aza-(1R,4R)-bicyclo[2.2.2]oct-(5Z)ene-3-(R)-carboxylic acid ethyl ester (1.22 g, 4.28 mmol) in THF (20 mL) at 0 °C with a THF solution of osmium tetroxide (109 mg, 0.43 mmol), followed by 4-methylmorpholine N-oxide (601 mg, 5.14 mmol). Stir the reaction at 0 °C for 1 h and at RT overnight. Quench the reaction with 10% aqueous sodium sulfite (20 mL), dilute the reaction mixture with ethyl acetate (100 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 20:80 to 1:1 ethyl acetate:hexanes) to give the title compound (0.8 g, 58%).

Preparation 25

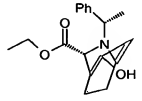
(5S,6R)-Difluoro-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester



Treat a solution of (5R,6S)-dihydroxy-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester (800 mg, 2.50 mmol) in dichloromethane (16 mL) at –10 °C with (diethylamino)sulfur trifluoride (0.786 mL, 6.0 mmol) for 1 h and at RT overnight. Quench the reaction with ice and saturated aqueous sodium bicarbonate. Extract with dichloromethane (100 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 15:85 ethyl acetate:hexanes) to give the title compound (480 mg, 60%).

Preparation 26

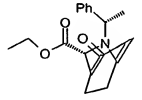
5-(S)-Hydroxy-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester



Add a solution of 2-[1-(S)-phenylethyl]-2-aza-(1R,4R)-bicyclo[2.2.2]oct-(5Z)ene-3-(R)-carboxylic acid ethyl ester (1.1 g, 3.86 mmol) in THF (5 mL) to a THF solution of boron trifluoride-methyl sulfide complex solution at 0 °C. Stir the reaction at 0 °C for 1 h, RT for 2 h and 30 °C for 30 min. Treat the reaction mixture with water (0.2 mL), 1 N NaOH (0.70 mL), THF (1.5 mL), ethanol (0.4 mL), 30% hydrogen peroxide (0.4 mL). Stir the reaction mixture at RT for 1 h. Extract the product with ethyl acetate, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 30:70 to 60:40 ethyl acetate:hexanes) to give the title compound (0.36 g, 30%).

Preparation 27

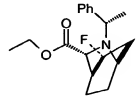
5-Oxo-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester



Treat a solution of 5-(S)-hydroxy-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester (252 mg, 0.83 mmol) in dichloromethane (10 mL) with Dess-Martin reagent (528 mg, 1.25 mmol) at RT for 2 h. Quench the reaction with 10% aqueous sodium sulfite solution and extract the product with ethyl acetate (50 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 30:70 to 60:40 ethyl acetate:hexanes) to give the title compound (120 mg, 48%).

Preparation 28

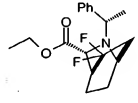
5-(R)-Fluoro-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester



Treat a solution of 5-(S)-hydroxy-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester (102 mg, 0.34 mmol) in dichloromethane (10 mL) at 0 °C with (diethylamino)sulfur trifluoride (53 µL, 0.40 mmol) for 2h. Quench the reaction with ice. Extract the product with dichloromethane (50 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 10:90 to 20:80 ethyl acetate:hexanes) to give the title compound (36 mg, 34%). **A-6**

Preparation 29

5,5-Difluoro-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester



Treat a solution of 5-oxo-2-[1-(S)-phenylethyl]-2-aza-(1R,4S)-bicyclo[2.2.2]octane-3-(R)-carboxylic acid ethyl ester (102 mg, 0.34 mmol) in dichloromethane (10 mL) at 0 °C with (diethylamino)sulfur trifluoride (111 µL, 0.85 mmol) for 1 h. Stir the reaction at RT overnight. Quench the reaction with ice and extract the product with ethyl acetate (50 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 10:90 to 20:80 ethyl acetate:hexanes) to give the title compound (40 mg, 37%).

Preparation 30

3-[2-Amino-1-hydroxy-3-phenylpropyl]-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester (Isomer I)

2-Aza-(1R,4R)-bicyclo[2.2.2]octane-2,3-dicarboxylic acid 2-tert-butyl ester 3-(R)-ethyl ester

Add di-tert-butyl dicarbonate (478 mg, 2.2 mmol) to an ethanol (10 mL) and ethyl acetate (5 mL) solution of 2-[1-(S)-phenylethyl]-2-aza-(1R,4R)-bicyclo[2.2.2]oct-(5Z)ene-3-(R)-carboxylic acid ethyl ester (570 mg, 2 mmol). Cool the reaction to –78 °C and add 10% palladium on carbon (424 mg, 0.40 mmol) to the reaction mixture and stir under an atmosphere of hydrogen gas (1 atm) overnight at RT. Filter the catalyst, concentrate the filtrate and purify (silica gel chromatography, eluting with 10:90 to 15:85 ethyl acetate:hexanes) to give the title compound (355 mg, 62%).

3-(R)-Hydroxymethyl-2-aza-(1R,4R)-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester

Treat a solution of 2-aza-(1R,4R)-bicyclo[2.2.2]octane-2,3-dicarboxylic acid 2-tert-butyl ester 3-(R)-ethyl ester (600 mg, 2.12 mmol) in dichloromethane (10 mL) at –78 °C with diisobutylaluminum hydride (1.0 M in dichloromethane, 5.3 mL, 5.3 mmol). Stir the reaction at –78 °C for 2 h and at RT overnight. Quench the reaction with a saturated aqueous sodium tartrate solution (30 mL over 30 min). Extract with ethyl acetate (75 mL) and purify (silica gel chromatography, eluting with 20:80 to 60:40 ethyl acetate:hexanes) to give the title compound (380 mg, 74%) along with 3-formyl-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester (68 mg, 13%).

3-(R)-Formyl-2-aza-(1R,4R)-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester

Treat a solution of 3-(R)-hydroxymethyl-2-aza-(1R,4R)-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester (570 mg, 2.37 mmol) in dichloromethane (16 mL) with Dess-Martin reagent (1.20 g, 2.84 mmol) at RT for 1.5 h. Quench the reaction with 10% aqueous sodium sulfite solution. Extract with ethyl acetate (75 mL), wash the organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 15:85 ethyl acetate:hexanes) to give the title compound (390 mg, 68%).

3-(2-Nitro-1-hydroxy-3-phenylpropyl)-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester-Isomer 1 and 3-(2-nitro-1-hydroxy-3-phenylpropyl)-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester-Isomer 2

Dissolve 3-(R)-formyl-2-aza-(1R,4R)-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester (70 mg, 0.3mmol) in anhydrous THF (0.7mL) and cool to 0 °C. Add a solution of tetrabutylammonium fluoride (1.0 M solution in THF, 0.03mL) and then dropwise add 1-phenyl-2-nitroethane (66 mg. 0.43mmol) to the mixture at 0 °C. Maintain the reaction at the same temperature with stirring under nitrogen gas. Dilute the mixture with ethyl acetate (20 mL) after 4 h and wash with saturated aqueous sodium chloride solution, extract the organic layer, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 2:98 ethyl acetate:dichloromethane) to give the two isomers: Isomer 1 (22 % yield) eluting with $R_f = 0.4$ and Isomer 2 (15 % yield) eluting with $R_f = 0.2$.

Isomer 1: MS (ES): $m/z = 389.2$ [M-H], Isomer 2: MS (ES): $m/z = 389.0$ [M-H].

3-[2-Amino-1-hydroxy-3-phenylpropyl]-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester-Isomer 1

Dissolve 3-(S)-[1-hydroxy-2-nitro-3-phenylpropyl]-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester-Isomer 1 (60 mg, 0.15mmol) in methanol (3 mL). Add nickel (II) chloride (29.7 mg. 0.23mmol) to the mixture at RT with vigorous stirring for 2 h. Cool the solution to 0 °C and add sodium borohydride (29 mg, 0.77 mmol). After 5 min at the same temperature, quench the reaction with water (3 mL) and concentrate. Dilute the residue with ethyl acetate and wash the organic layer with water, extract the organic layer and dry (magnesium sulfate). Filter and concentrate to obtain the crude title compound which is used in the next step without further purification.

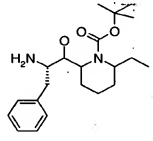
MS (ES): $m/z = 361.3$ [M+H].

The compounds of Preparation 31-33 may be prepared essentially as described in Preparation 30 with Preparations 32-33 using cyclopentadiene as described in Preparation 23.

		MS

Prep	Compound	[M+H]
30	3-[2-Amino-1-hydroxy-3-phenylpropyl]-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester-Isomer 2	361.2
31	3-(2-Amino-1-hydroxy-3-phenylpropyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester-Isomer 1	347.3
32	3-(2-Amino-1-hydroxy-3-phenylpropyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester-Isomer 2	347.2

Preparation 33



2-((2S)-2-Amino-1-hydroxy-3-phenylpropyl)-6-ethylpiperidine-1-carboxylic acid tert-butyl ester

2-Ethylpiperidine-1-carboxylic acid tert-butyl ester

Stir 2-ethylpiperidine (11.8 mL, 88.3 mmol) and di-tert-butyl-dicarbonate (23.1 g, 105.96 mmol) in saturated aqueous sodium bicarbonate (100 mL)and 1,4-dioxane (100 mL) at RT overnight. Extract with ethyl acetate; wash the combined organic layers with 5% aqueous potassium bisulfate, water, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 90:10 hexanes:ethyl acetate) to give the title compound (12 g, 64%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, J=7.26 Hz, 3H), 1.43 (s, 9H), 1.20-1.80 (m, 6H), 2.64-2.78 (m, 1H), 3.95 (br d, 1H), 4.09 (br s, 1H).

2-((2S)-2-Dibenzylamino-1-hydroxy-3-phenylpropyl)-6-ethylpiperidine-1-carboxylic acid tert-butyl ester

Add N,N,N',N'-tetramethylethylendiamine (1.4 mL, 9.11 mmol), then sec-butyllithium (1.4 M in cyclohexane, 7.2 mL, 10.1 mmol) to 2-ethylpiperidine-1-carboxylic acid tert-butyl ester in diethyl ether (18 mL) at –78 °C under a nitrogen atmosphere. Warm to -35 °C and stir for 1 h. Cool to –78 °C and add (2S)-2-

(dibenzylamino)-3-phenylpropanal (3.0 g, 9.11 mmol) in diethyl ether (4 mL) and stir for 30 min. Quench at –78 °C with water, warm to RT and extract with diethyl ether. Combine the organic layers, dry (magnesium sulfate) and concentrate. Separate the two major diastereomers of 2-((2S)-2-dibenzylamino-1-hydroxy-3-phenylpropyl)-6-ethylpiperidine-1-carboxylic acid tert-butyl ester using normal-phase preparative HPLC.
Isomer 1: MS (ES): m/z = 543 [M+H].
Isomer 2: MS (ES): m/z = 543 [M+H].

2-((2S)-2-Amino-1-hydroxy-3-phenylpropyl)-6-ethylpiperidine-1-carboxylic acid tert-butyl ester

Stir 2-((2S)-2-dibenzylamino-1-hydroxy-3-phenylpropyl)-6-ethylpiperidine-1-carboxylic acid tert-butyl ester-Isomer 2 (0.7 g, 1.23 mmol) and 20% palladium hydroxide (0.2 g, 50% wet) in methanol (10 mL) under a balloon of hydrogen gas at RT for 2 days. Filter the suspension through a pad of filtering agent, wash with methanol and concentrate to give the title compound (0.4 g, 95%).
MS (ES): m/z = 363 [M+H].

Preparation 34

(S)-2-sec-Butylamino-6-(cyclopropanesulfanyl-methylamino)-isonicotinic acid

Cyclopropanesulfonic acid methylamide

Dissolve cyclopropylsulfonyl chloride (1.0 g, 7.1 mmol) in dichloromethane (8 mL). Cool to 0 °C and slowly add methylamine (2.0 M solution in THF, 10.7 mL, 21 mmol). Stir for 5 min and add triethylamine dropwise (1.4 mL, 11 mmol). Stir from 0 °C to RT overnight. Filter, concentrate the organic layer and purify (silica gel chromatography, eluting with 0:100 to 25:75 ethy acetate:hexanes) to give the title compound.
MS (ES): m/z = 134 [M-H].

Sodium cyclopropanesulfonic acid methylamide

Dissolve cyclopropanesulfonic acid methylamide in THF (10 mL) and cool to 0 °C. Slowly add sodium hydride (208 mg, 60 % suspension in mineral oil) into the

solution and stir from 0 °C to RT for 3 h. Concentrate and use the solid in the next step without further purification.

(S)-2-sec-Butylamino-6-chloro-isonicotinic acid methyl ester

Dissolve 2,6-dichloro-isonicotinic methyl ester (2.0 g, 10 mmol), palladium (II) acetate (224.0 mg, 1.0 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (632 mg, 1.0 mmol) and cesium carbonate (3.96 g, 12 mmol) in toluene (20 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen gas. Add (S)-(+)-sec-butylamine (1.2 mL, 12 mmol) to the solution and heat the sealed mixture overnight at 100 °C. Cool to RT and dilute with diethyl ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the title compound (73%).
MS (ES): *m/z* = 243 [M+H].

(S)-2-sec-Butylamino-6-(cyclopropanesulfonyl-methylamino)-isonicotinic acid methyl ester

Dissolve (S)-2-sec-butylamino-6-chloro-isonicotinic acid methyl ester (880 mg, 3.6 mmol), tris(dibenzylideneacetone)dipalladium (0) (164 mg, 0.18 mmol), 2-(di-tert-butylphosphino)biphenyl (107 mg, 0.36 mmol) in toluene (18 mL) and THF (2 mL) in a previously nitrogen-filled sealed vessel. Add sodium cyclopropanesulfonic acid methylamide (700 mg, 4.42 mmol) into the mixture under nitrogen and flush the reactants again with nitrogen before sealing and heating overnight at 100 °C. Cool the reaction to RT and dilute with ethyl acetate and diethyl ether and filter through a filtering agent. Concentrate and purify (silica gel chromatography, eluting with 0:100 to 08:92 ethyl acetate:hexanes) to give the title compound.
MS (ES): *m/z* = 342 [M+H].

(S)-2-sec-Butylamino-6-(cyclopropanesulfonyl-methylamino)-isonicotinic acid

Dissolve (S)-2-sec-butylamino-6-(cyclopropanesulfonyl-methylamino)-isonicotinic acid methyl ester (600 mg, 1.97 mmol) in methanol (18 mL). Slowly add 2 N NaOH (3 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 with 5 N HCl and concentrate. Dilute with ethyl acetate (30 mL) and wash the organic layer with

saturated aqueous sodium chloride solution, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): *m/z* = 328 [M+H].

The compounds of Preparation 35-41 may be prepared essentially as described in Preparation 35 starting with the corresponding sulfonyl chlorides and amines.

Prep	Compound	MS (ES) [M+H]
35	(S)-2-sec-Butylamino-6-(cyclopropyl-methanesulfonylamino)-isonicotinic acid	328
36	(S)-2-sec-Butylamino-6-(propane-2-sulfonylamino)-isonicotinic acid	316
37	(S)-2-sec-Butylamino-6-[methyl-(propane-2-sulfonyl)-amino]-isonicotinic acid	330
38	(S)-2-sec-Butylamino-6-(ethyl-methanesulfonylamino)-isonicotinic acid	316
39	(S)-2-sec-Butylamino-6-[(2-fluoroethyl)-methanesulfonylamino]-isonicotinic acid	334
40	(S)-2-sec-Butylamino-6-[(2,2-difluoroethyl)-methanesulfonylamino]-isonicotinic acid	352
41	(S)-2-sec-Butylamino-6-[(2,2,2-trifluoroethyl)-methanesulfonylamino]-isonicotinic acid	370

Preparation 42

(S)-2-sec-Butylamino-6-[1,3]dioxan-2-yl-isonicotinic acid

2-Chloro-6-vinyl-isonicotinic acid methyl ester

Add methyl 2,6-dichloro-isonicotinate (3.8 g, 18.4 mmol), tetrakis(triphenylphosphine)palladium (0) (1.15 g, 0.99 mmol), triphenyhlphosphine (524 mg, 2 mmol) in toluene (40 mL) to a previously nitrogen-filled sealed vessel. Flush the reactants with nitrogen again. Add tributyl(vinyl)tin (6.98 mL, 24.0 mmol) and heat the sealed mixture at 95 °C overnight. Cool to RT, dilute with diethyl ether and filter through a filtering agent. Wash the organic filtrate with saturated ammonium chloride, saturated sodium bicarbonate and saturated aqueous sodium chloride. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 5:95 to 10:90 ethyl acetate:hexanes) to give the title compound (70%).

2-Chloro-6-formyl-isonicotinic acid methyl ester

Dissolve 2-chloro-6-vinyl-isonicotinic acid methyl ester (1.6 g, 8 mmol) in dichloromethane (10 mL) and flush the reaction vessel with oxygen gas. Cool to –78 °C and pass positive pressure of ozone through the solution for 15 min until blue color appears. Quench with excess dimethylsulfide (1.5 mL) and warm to RT overnight. Concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the title compound.

2-Chloro-6-[1,3]dioxan-2-yl-isonicotinic acid methyl ester

Dissolve 2-chloro-6-formyl-isonicotinic acid methyl ester (200 mg, 1.0 mmol) in THF (8 mL). Add Amberlyst® 15 ion exchange resin (0.3 g) and dropwise 1,3-propanediol (0.1 mL, 1.5 mmol). Stir at RT for two days. Filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the title compound (88%).

(S)-2-sec-Butylamino-6-[1,3]dioxan-2-yl-isonicotinic acid methyl ester

Dissolve 2-chloro-6-[1,3]dioxan-2-yl-isonicotinic acid methyl ester (150 mg, 0.6 mmol), palladium (II) acetate (7.0 mg, 0.03 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (20 mg, 0.03 mmol) and cesium carbonate (482 mg, 1.3 mmol) in toluene

(2 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen gas. Add (S)-(+)-sec-butylamine (0.074 mL, 0.74 mmol) and heat the sealed mixture overnight at 100 °C. Cool to RT, dilute with diethyl ether and filter through filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the title compound (68%).

(S)-2-sec-Butylamino-6-[1,3]dioxan-2-yl-isonicotinic acid

Dissolve (S)-2-sec-butylamino-6-[1,3]dioxan-2-yl-isonicotinic acid methyl ester (100 mg, 0.35 mmol) in methanol (4 mL). Slowly add 1 N lithium hydroxide (0.46 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 with 5 N HCl and concentrate. Dilute with ethyl acetate (15 mL), wash the organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): *m/z* = 281 [M+H].

The compound of Preparation 43 may be prepared essentially as described in Preparation 42.

Prep	Compound	MS (ES) [M+H]
43	(S)-2-sec-Butylamino-6-[1,3]dioxolan-2-yl-isonicotinic acid	267

Preparation 44

(S)-2-sec-Butylamino-6-difluoromethyl-isonicotinic acid

2-Chloro-6-vinyl-isonicotinic acid methyl ester

Add methyl 2,6-dichloroisonicotinate (3.8 g, 18.4 mmol), tetrakis(triphenylphosphine)palladium (0) (1.15 g, 0.99 mmol), triphenyhlphosphine (524 mg, 2 mmol) and toluene (40 mL) in a previously nitrogen-filled sealed vessel. Flush the reactants with nitrogen again. Add tributyl(vinyl)tin (6.98 mL, 24.0 mmol) under nitrogen and heat the sealed mixture at 95°C overnight with vigorous stirring. Cool the reaction to RT, dilute with diethyl ether and filter through a filtering agent. Wash the organic filtrate with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and

purify (silica gel chromatography, eluting with 5:95 to 10:90 ethyl acetate:hexanes) to give the title compound (70%).

2-Chloro-6-formyl-isonicotinic acid methyl ester

Dissolve 2-chloro-6-vinyl-isonicotinic acid methyl ester (1.6 g, 8 mmol) in dichloromethane (10 mL) and flush the reaction vessel with oxygen gas. Cool to –78 °C and pass positive pressure of ozone through the solution for 15 min until sky blue color appears. At the same temperature quench the reaction with excess dimethylsulfide (1.5 mL) and warm up to RT overnight. Concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the title compound.

2-Chloro-6-difluoromethyl-isonicotinic acid methyl ester

Dissolve 2-chloro-6-formyl-isonicotinic acid methyl ester (386 mg, 1.93 mmol) in dichloromethane (2 mL) and cool to 0 °C. Add (diethylamino)sulfur trifluoride (0.625 mL, 4.8 mmol) dropwise and stir overnight while warming up to RT. Quench the reaction by water and dilute further with dichloromethane (10 mL). Extract the organic layer and dry (magnesium sulfate). Concentrate and purify (silica gel chromatography, eluting with 5:95 ethyl acetate:hexanes) to give the title compound as an oil (47%).

(S)-2-sec-Butylamino-6-difluoromethyl-isonicotinic acid methyl ester

Dissolve 2-chloro-6-difluoromethyl-isonicotinic acid methyl ester (200 mg, 0.9 mmol), palladium (II) acetate (20.0 mg, 0.09 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (56 mg, 0.09 mmol) and cesium carbonate (438 mg, 1.35 mmol) in toluene (3 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen gas. Add (S)-(+)-sec-butylamine (0.108 mL, 1.08 mmol) to the solution under nitrogen and heat the sealed mixture overnight at 100 °C. Cool the reaction to RT. Dilute with diethyl ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 10:90 acetate:hexanes) to give the title compound as an oil (60%).

(S)-2-sec-Butylamino-6-difluoromethyl-isonicotinic acid

Dissolve 2-sec-butylamino-6-difluoromethyl-isonicotinic acid methyl ester (140 mg, 0.54 mmol) in methanol (2 mL) and THF (10 mL). Slowly add 1 N aqueous lithium hydroxide (0.7 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 by 5 N HCl and concentrate to near dryness. Dilute with ethyl acetate (20 mL) and wash the organic layer with saturated aqueous sodium chloride. Dry (magnesium sulfate) and concentrate to give the title compound as a solid.

Preparation 45

(S)-2-sec-Butylamino-6-(1,1-difluoroethyl)-isonicotinic acid

2-Acetyl-6-chloro-isonicotinic acid methyl ester

Add methyl 2,6-dichloroisonicotinate (3.0 g, 15.0 mmol), trans-dichlorobis(triphenylphosphine)palladium (II) (105 mg, 0.15 mmol) and toluene (10 mL) in a previously nitrogen filled sealed vessel. Flush the reactants with nitrogen again. Add tributyl(1-ethoxyvinyl)tin (5.57 mL, 16.5 mmol) under nitrogen and heat the sealed mixture at 100 °C overnight with vigorous stirring. Cool the reaction to RT, dilute with diethyl ether and filter through a filtering agent. Concentrate to near dryness and dilute the residue with THF (10 mL). Add dropwise 5 N HCl (5 mL) and stir the mixture overnight. Concentrate to near dryness and extract the organic material by diethyl ether, partitioning with water. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the title compound as a solid over two steps (47%).

2-Chloro-6-(1,1-difluoroethyl)-isonicotinic acid methyl ester

Dissolve 2-acetyl-6-chloro-isonicotinic acid methyl ester (410 mg, 1.9 mmol) in dichloromethane (4 mL) and cool to 0 °C. Add (diethylamino)sulfur trifluoride (0.55 mL, 4.2 mmol) dropwise and stir over night while warming up to RT. Quench the reaction using water and dilute further with dichloromethane (10 mL). Extract the organic layer and dry (magnesium sulfate). Concentrate and purify (silica gel chromatography, eluting with 5:95 ethyl acetate:hexanes) to give the title compound as an oil (45%).

(S)-2-sec-Butylamino-6-(1,1-difluoroethyl)-isonicotinic acid methyl ester

Dissolve 2-chloro-6-(1,1-difluoroethyl)-isonicotinic acid methyl ester (200 mg, 0.85 mmol), palladium (II) acetate (20.0 mg, 0.09 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (56 mg, 0.09 mmol) and cesium carbonate (414 mg, 1.27 mmol) in toluene (3 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen gas. Add (S)-(+)-sec-butylamine (0.10 mL, 1.02 mmol) to the solution under nitrogen and heat the sealed mixture overnight at 100 °C. Cool the reaction to RT. Dilute with diethyl ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 5:95 ethyl acetate:hexanes) to give the title compound as an oil (86%).

(S)-2-sec-Butylamino-6-(1,1-difluoroethyl)-isonicotinic acid

Dissolve (S)-2-sec-butylamino-6-(1,1-difluoroethyl)-isonicotinic acid methyl ester (200 mg, 0.73 mmol) in methanol (3 mL). Slowly add 1 N lithium hydroxide (1.0 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 by 5 N HCl and concentrate to near dryness. Dilute with ethyl acetate (20 mL) and wash the organic layer with saturated aqueous sodium chloride. Dry (magnesium sulfate) and concentrate to give the title compound as a solid (95%).

MS (ES): m/z = 259 [M+H].

Preparation 46

(S)-2-sec-Butylamino-6-(2-oxopropyl)-isonicotinic acid

2-Chloro-6-(2-oxopropyl)-isonicotinic acid methyl ester

Add methyl 2,6-dichloroisonicotinate (3.0 g, 15.0 mmol), trans-dichlorobis(tri-o-tolylphosphine)palladium (II) (196 mg, 0.25 mmol), tributyltin methoxide (2.4 g, 7.5 mmol) and toluene (20 mL) in a previously nitrogen filled sealed vessel. Flush the reactants with nitrogen again. Add isopropenyl acetate (0.85 mL, 7.75 mmol) under nitrogen and heat the sealed mixture at 100 °C overnight with vigorous stirring. Cool the reaction to RT, dilute with diethyl ether and filter through a filtering agent. Concentrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the title compound (29%).

(S)-2-sec-Butylamino-6-(2-oxopropyl)-isonicotinic acid methyl ester

Dissolve 2-chloro-6-(2-oxopropyl)-isonicotinic acid methyl ester (200 mg, 0.88 mmol), palladium (II) acetate (2.0 mg, 0.009 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (8.2 mg, 0.014 mmol) and cesium carbonate (458 mg, 1.23 mmol) in toluene (2 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen gas. Add (S)-(+)-sec-butylamine (0.105 mL, 1.0 mmol) to the solution under nitrogen and heat the sealed mixture overnight at 100 °C. Cool the reaction to RT. Dilute with diethyl ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, 0:100 to 20:80 ethyl acetate:hexanes) to give the title compound (22%).

MS (ES): $m/z = 265$ [M+H].

(S)-2-sec-Butylamino-6-(2-oxopropyl)-isonicotinic acid

Dissolve (S)-2-sec-butylamino-6-(2-oxopropyl)-isonicotinic acid methyl ester (50 mg, 0.19 mmol) in THF (2 mL). Slowly add 1 N lithium hydroxide (0.28 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 by 5 N HCl and concentrate to near dryness. Dilute with ethyl acetate (10 mL) and wash the organic layer with saturated aqueous sodium chloride. Dry (magnesium sulfate) and concentrate to give the title compound as a solid.

MS (ES): $m/z = 251$ [M+H].

Preparation 47

(S)-2-sec-Butylamino-6-(2,2-difluoropropyl)-isonicotinic acid

2-Chloro-6-(2,2-difluoropropyl)-isonicotinic acid methyl ester

Dissolve 2-chloro-6-(2-oxopropyl)-isonicotinic acid methyl ester (760 mg, 3.3 mmol in dichloromethane (5 mL) and cool to 0 °C. Add (diethylamino)sulfur trifluoride (1.1 mL, 8.3 mmol) dropwise and stir over night while warming up to RT. Quench with water and dilute further with dichloromethane (20 mL). Extract the organic layer and dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 5:95 ethyl acetate:hexanes) to give the title compound as an oil (18%).

(S)-2-sec-Butylamino-6-(2,2-difluoropropyl)-isonicotinic acid methyl ester

Dissolve 2-chloro-6-(2,2-difluoropropyl)-isonicotinic acid methyl ester (150 mg,

0.6 mmol), palladium (II) acetate (224.0 mg, 1.0 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (37 mg, 0.06 mmol) and cesium carbonate (293 mg, 0.9 mmol) in toluene (2 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen gas. Add (S)-(+)-sec-butylamine (0.07 mL, 0.72 mmol) to the solution under nitrogen and heat the sealed mixture overnight at 100 °C. Cool the reaction to RT. Dilute with diethyl ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 5:95 ethyl acetate:hexanes) to give the title compound as an oil (58%).

(S)-2-sec-Butylamino-6-(2,2-difluoropropyl)-isonicotinic acid

Dissolve (S)-2-sec-butylamino-6-(2,2-difluoropropyl)-isonicotinic acid methyl ester (100 mg, 0.34 mmol) in THF (3 mL). Slowly add 1 N lithium hydroxide (0.52 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 by 5 N HCl and concentrate to near dryness. Dilute with ethyl acetate (20 mL) and wash the organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a solid.

Preparation 48

2-Acetyl-(S)-6-sec-butylamino-isonicotinic acid

2-Acetyl-(S)-6-sec-butylamino-isonicotinic acid methyl ester

Dissolve 2-acetyl-6-chloro-isonicotinic acid methyl ester (300 mg, 1.4 mmol), palladium (II) acetate (16 mg, 0.07 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (46 mg, 0.07 mmol) and cesium carbonate (781 mg, 2.1 mmol) in anhydrous toluene (3 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen gas. Add (S)-(+)-sec-butylamine (0.16 mL, 1.68 mmol) to the solution under nitrogen and heat the sealed mixture overnight at 100 °C. Cool the reaction to RT. Dilute with diethyl ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 5:95 ethyl acetate:hexanes) to give the title compound as a solid (17%).

2-Acetyl-(S)-6-sec-butylamino-isonicotinic acid

Dissolve 2-acetyl-(S)-6-sec-butylamino-isonicotinic acid methyl ester (60 mg, 0.24 mmol) in THF (3 mL). Slowly add 1 N lithium hydroxide (0.3 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 by 5 N HCl and concentrate to near dryness. Dilute with ethyl acetate (15 mL) and wash the organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a solid (96%).

MS (ES): m/z = 237 [M+H].

Preparation 49

(S)-6-sec-Butylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester

2-Chloro-6-(1-ethoxyvinyl)-isonicotinic acid methyl ester

Add methyl 2,6-dichloroisonicotinate (2.06 g, 10 mmol), tetrakis(triphenylphosphine)palladium (0) (578 mg, 0.5 mmol), triphenyhlphosphine (263 mg, 1 mmol) and toluene (25 mL) in a previously nitrogen filled sealed vessel. Flush the reactants with nitrogen again. Add tributyl(1-ethoxyvinyl)tin (4.05 mL, 12.0 mmol) under nitrogen and heat the sealed mixture at 100 °C overnight with vigorous stirring. Cool the reaction to RT, dilute with diethyl ether and filter through a filtering agent. Wash the organic filtrate with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride respectively. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 5:95 to 10:90 ethyl acetate:hexanes) to give the title compound.

6-Chloropyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester

Dissolve 2-chloro-6-(1-ethoxyvinyl)-isonicotinic acid methyl ester (4.8 g, 20 mmol) in dichloromethane (40 mL) and flush the reaction vessel with oxygen gas. Cool to –78°C and pass positive pressure of ozone through the solution for 10 min until sky blue color appears. At the same temperature quench the reaction with excess dimethylsulfide (6 mL) and warm up to RT overnight. Concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the title compound.

(S)-6-sec-Butylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester

Dissolve 6-chloropyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (2.8 g, 11.5 mmol), palladium (II) acetate (258.0 mg, 1.15 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (716 mg, 1.15 mmol) and cesium carbonate (5.6 g, 17.2 mmol) in toluene (25 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen gas. Add (S)-(+)-sec-butylamine (1.38 mL, 13.8 mmol) to the solution under nitrogen and heat the sealed mixture overnight at 100 °C. Cool the reaction to RT. Dilute with diethyl ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the title compound as an oil (72%).

(S)-6-sec-Butylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester alternatively may be prepared by the following procedure.

2-Chloro-6-methoxy-isonicotinic acid methyl ester

Mix commercially available 2-chloro-6-methoxy-isonicotinic acid (17 g, 90.6 mmol), concentrated sulfuric acid (0.85 mL) in methanol (150 mL) and reflux overnight. Cool the mixture to RT, filter and dry the solid under vacuum to give the title compound (15.5 g). Concentrate filtrate and dilute with ethyl acetate (150 mL). Wash with sodium bicarbonate solution, water, dry (sodium sulfate) and concentrate to give additional title compound (1.7 g) (17.2 g, 93% combined yield).
MS (ES): m/z = 202 [M+H].

6-Methoxypyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester

Add 2-chloro-6-methoxy-isonicotinic acid methyl ester (5 g, 24.8 mmol), palladium acetate (4.157 g, 18.5 mmol), 1,4-bis(diphenylphosphino)butane (1.038 g, 2.43 mmol), ethanol (127 mL), triethylamine (18 mL, 129 mmol) with DMSO (150 mL) to a pressure vessel. Seal the pressure vessel and purge with nitrogen. Pressurize the reaction mixture with carbon monoxide (690 KPa), seal the vessel, agitate the reaction and heat to 80 °C for 19 h. Cool to RT, filter the reaction mixture through a filtering agent and concentrate. Dissolve the residue in water (200 mL) and extract with hexanes (3 x 150 mL) and concentrate to give 6-methoxypyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (3.5 g). Extract the aqueous layer with ethyl acetate (3 x 150 mL) and wash

the combined ethyl acetate layers with water, aqueous sodium bicarbonate solution, saturated aqueous sodium chloride, dry (sodium sulfate), concentrate, and purify (silica gel chromatography, eluting with ethyl acetate and hexanes) to give additional title compound (2.1 g) (5.6 g, 95% combined yield).
MS (ES): m/z = 240 [M+H].

6-Chloropyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester

Mix 6-methoxypyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (239 mg, 1.0 mmol), phosphorous oxychloride (0.46 mL, 4.93 mmol) in DMF (1.9 mL) and heat to 85 °C for 24 h. Cool to RT and quench with saturated aqueous sodium acetate solution (5 mL). Extract with ethyl acetate, wash with water, dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with ethyl acetate and hexanes) to give the title compound (190 mg, 78%).
MS (ES): m/z = 244 [M+H].

(S)-6-sec-Butylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester

Add 6-chloropyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (2.44 g, 10 mmol), palladium acetate (224 mg, 1.0 mmol), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (623 mg, 1.0 mmol), cesium carbonate (4.95 g, 15.2 mmol) in toluene (70 mL) in a sealed tube. Degas the tube for 5 min with nitrogen, add (S)-sec-butylamine (1.2 mL, 11.8 mmol) and seal the tube. Heat to 80 °C overnight. Cool to RT and filter the mixture through a filtering agent. Wash with ethyl acetate. Dissolve the solid in water and extract with ethyl acetate. Combine all organic solutions, concentrate and purify (silica gel chromatography, eluting with ethyl acetate and hexanes) to give the title compound (2.5g, 90%).
MS (ES): m/z = 281 [M+H].

(S)-6-sec-Butylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester

Dissolve (S)-6-sec-butylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (990 mg, 3.5 mmol) in THF (35 mL) and dropwise add 1 N lithium hydroxide solution (3.5 mL). Stir at RT for 2 h and acidify the mixture to about pH = 4 by 5 N HCl and concentrate to near dryness. Dilute with ethyl acetate (20 mL) and wash

the organic layer with saturated sodium chloride solution, dry (magnesium sulfate) and concentrate to give a 2:1 ratio of crude title compound to starting material which is used in the next step without further purification.

Preparation 50

(S)-2-sec-Butylamino-6-cyano-isonicotinic acid

(S)-2-sec-Butylamino-6-cyano-isonicotinic acid methyl ester

Dissolve (S)-2-sec-butylamino-6-chloro-isonicotinic acid methyl ester (800 mg, 0.34 mmol), tris(dibenzylideneacetone)dipalladium (0) (120 mg, 0.13 mmol), 1,1'-bis(diphenylphosphino)ferrocene (146 mg, 0.26 mmol), zinc dust (52 mg) and zinc (II) cyanide (387 mg, 3.3 mmol) in N,N-dimethylacetamide (6.6 mL)) in a previously nitrogen-filled sealed vessel. Flush the reactants with nitrogen before sealing and heat for 6 h at 130 °C. Cool to RT, dilute with ethyl acetate and wash with 2 N ammonium hydroxide. Wash the organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 05:95 ethyl acetate:hexanes) to give the title compound.

(S)-2-sec-Butylamino-6-cyano-isonicotinic acid

Dissolve (S)-2-sec-butylamino-6-cyano-isonicotinic acid methyl ester (250 mg, 0.93 mmol) in methanol (3 mL). Slowly add 2 N NaOH (1.5 mL) and stir overnight at RT. Acidify to about pH = 6 with 5 N HCl and concentrate. Dilute with ethyl acetate (20 mL) and wash the organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): m/z = 220 [M+H].

Preparation 51

(S)-2-sec-Butylamino-6-methanesulfonyl-isonicotinic acid

(S)-2-sec-Butylamino-6-methylsulfanyl-isonicotinic acid methyl ester

Add toluene (20 mL), (S)-2-sec-butylamino-6-chloro-isonicotinic acid methyl ester (2.01 g, 8.29 mmol), palladium acetate (186mg, 0.83mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (516mg, 0.83mmol), cesium carbonate (5.40g, 16.6mmol), and sodium thiomethoxide (1.16 g, 16.6 mmol) to a sealed vessel flushed

with nitrogen. Heat the sealed vessel at 90 °C overnight. Cool to RT and filter the solution through a filtering agent and concentrate the filtrate. Purify the residue (silica gel chromatography, eluting with ethyl acetate:hexanes 90:10) to give the title compound (1.4 g, 66%).

MS (ES): *m/z* = 255 [M+H].

(S)-2-sec-Butylamino-6-methanesulfonyl-isonicotinic acid methyl ester

Chill a solution of (S)-2-sec-butylamino-6-methylsulfanyl-isonicotinic acid methyl ester (1.22 g, 4.80 mmol) in dichloromethane (20 mL) in an ice bath and add 3-chloroperbenzoic acid (2.74 g, 15.9 mmol). Stir at RT for 3 h and partition the solution between dichloromethane and saturated sodium bicarbonate. Extract the aqueous layer with dichloromethane (2 x 30 mL). Combine the organic extract, wash with water, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel, eluting with ethyl acetate:hexanes 25:75) to give the title compound (1.02 g, 74%).

MS (ES): *m/z* = 287 [M+H].

(S)-2-sec-Butylamino-6-methanesulfonyl-isonicotinic acid

Chill a solution of (S)-2-sec-butylamino-6-methanesulfonyl-isonicotinic acid methyl ester (1.02 g, 3.57 mmol) in THF (10 mL) in an ice bath. Add 1 N lithium hydroxide (5.4 mL, 5.4 mmol) and stir the solution at RT for 3 h. Add 1 N HCl until about pH = 2. Concentrate and partition the residue between ethyl acetate and water. Separate the layers and extract the aqueous layer with ethyl acetate (2 x 30 mL). Wash the combined extract with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): *m/z* = 273 [M+H].

Preparation 52

(S)-2-sec-Butylamino-6-propanesulfonyl-isonicotinic acid

2-Chloro-6-propylsulfanyl-isonicotinic acid methyl ester

Add 2,6-dichloroisonicotinic acid methyl ester (4.12g, 20.0mmol), toluene (40 mL), palladium acetate (448mg, 2.0 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-

binaphthyl (1.25 g, 2.0 mmol) and cesium carbonate (7.82 g, 24.0 mmol) into a sealed vessel flushed with nitrogen. Slowly add propanethiol (2.2 mL, 24 mmol,). Heat and stir the reaction mixture at 80 °C for 18 h. Cool to RT, dilute with diethyl ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, 2:98 to 5:95 ethyl acetate:hexane) to give the title compound (55%).

2-Chloro-6-propanesulfonyl-isonicotinic acid methyl ester

Add a suspension of potassium peroxymonosulfate (35.6g, 57.7 mmol) in water (80 mL) to a cooled solution of 2-chloro-6-propylsulfanyl-isonicotinic acid methyl ester (4.71g, 19.2 mmol) in methanol (40 mL) and THF (40 mL). Stir the mixture at RT for 3 days. Dilute the mixture with water and extract with dichloromethane (3 x 100 mL). Wash the combined extracts with water, dry (magnesium sulfate), concentrate and purify (silica gel chromatograpy, eluting with 20:80 ethyl acetate:hexanes) to give the title product (2.75g, 52%).

(S)-2-sec-Butylamino-6-propanesulfonyl-isonicotinic acid methyl ester

Add 2-chloro-6-propanesulfonyl-isonicotinic acid methyl ester (2.70g, 9.71 mmol), toluene (40 mL), palladium acetate (218mg, 0.97mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (605mg, 0.97mmol), cesium carbonate (4.75g, 14.6mmol), and (S)-sec-butylamine (1.46 mL, 14.6 mmol) to a sealed vessel flushed with nitrogen. Heat and stir the sealed vessel at 90 °C overnight. Cool to RT, filter through a pad of filtering agent, concentrate and purify (silica gel chromatography, eluting with 20:80 to 30:70-ethyl acetate:hexanes) to give the title compound (2.47 g, 81%).
MS (ES): m/z = 315 [M+H].

(S)-2-sec-Butylamino-6-propanesulfonyl-isonicotinic acid

Add 2 N NaOH (6.0 mL, 12.0 mmol) to a solution of (S)-2-sec-butylamino-6-propanesulfonyl-isonicotinic acid methyl ester (2.47 g, 7.87 mmol) in methanol (10 mL) at 0 °C. Stir the mixture at RT for 3 h, acidify the solution to about pH = 2 and concentrate to one half of the solvent. Partition the residue between ethyl acetate and water. Extract the aqueous layer with ethyl acetate (2 x 50 mL). Wash the combined

extracts with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (90%).

MS (ES): *m/z* = 301 [M+H].

Preparation 53

(S)-2-sec-Butylamino-6-isopropanesulfonyl-isonicotinic acid

2-Chloro-6-isopropylsulfonyl-isonicotinic acid methyl ester

Add sodium isopropylthiolate (0.89g, 10.0 mmol, (prepared from treatment of isopropanethiol with 0.95 equivalent of sodium hydride) slowly to a solution of methyl 2,6-dichloroisonicotinate (2.06g, 10.0 mmol) in DMF (10 mL) at 0 °C. Stir the mixture at RT overnight. Partition the mixture between diethyl ether (30 mL) and water (30 mL) and extract the aqueous layer with diethyl ether (2 x 30 mL). Wash the combined extracts with 5% aqueous lithium hydroxide solution, dry (magnesium sulfate) and concentrate. The crude material is used directly in the next step reaction without further purification.

2-Chloro-6-isopropanesulfonyl-isonicotinic acid methyl ester

Add 3-chloroperbenzoic acid (5.32 g, 30.8 mmol) to a solution of 2-chloro-6-isopropylsulfanyl-isonicotinic acid methyl ester (2.37g, 9.63 mmol) in dichloromethane (50 mL) at 0 °C. Stir the mixture at RT for 4 h and partition the mixture between dichloromethane and aqueous saturated sodium bicarbonate. Extract the aqueous layer with dichloromethane (2 x 50 mL) and wash the combined organic extracts with water, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica-gel chromatography, eluting with 25:75 ethyl acetate:hexanes) to give the title compound (1.26 g, 47%).

(S)-2-sec-Butylamino-6-isopropanesulfonyl-isonicotinic acid methyl ester

Add 2-chloro-6-isopropanesulfonyl-isonicotinic acid methyl ester (1.26 g, 4.53 mmol), toluene (20 mL), palladium acetate (102mg, 0.453 mmol.), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (282 mg, 0.453mmol) and cesium carbonate (2.21 g, 6.80 mmol) to a sealed vessel flushed with nitrogen. Slowly add (S)-sec-butylamine (0.68 mL, 6.80 mmol) to the mixture. Heat and stir the sealed vessel at 90 °C

overnight. Cool to RT, concentrate and purify (silica gel chromatography, eluting with 20:80 to 70:30 ethyl acetate:hexanes) to give the title compound.

(S)-2-sec-Butylamino-6-isopropanesulfonyl-isonicotinic acid

Add 2 N NaOH (7.0 mL, 14.0 mmol) to a solution of 2-sec-butylamino-6-isopropanesulfonyl-isonicotinic acid methyl ester (1.46 g, 4.65 mmol) in methanol (10 mL) at 0 °C. Stir the mixture at RT for 3 h and acidify the solution to about pH = 2 and concentrate the solvent to one half volume. Partition the residue between ethyl acetate and water, and extract the aqueous layer with ethyl acetate (2 x 50 mL). Wash the combined organic extracts with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound in 90% yield.
MS (ES): m/z = 301 [M+H].

The compounds of Preparation 54-55 may be prepared essentially as described in Preparation 53.

Prep	Compound	MS (ES) [M+H]
54*	(S)-2-sec-Butylamino-6-cyclopropanesulfonyl-isonicotinic acid	299
55**	(S)-2-sec-Butylamino-6-cyclopentanesulfonyl-isonicotinic acid	327

* Sodium cyclopropylthiolate Add solid sulfur (0.47 g, 15.0 mmol) to a solution of cyclopropylmagnesium bromide (0.8 M, 20.0 mL, 16.0 mmol) in THF (20 mL) at 0 °C according to the reference J. Am. Chem. Soc., **114**(9), 3499, (1992). Heat at 50 °C for 3 h and cool to 0 °C. Add lithium aluminum hydride (0.49 g, 13.0 mmol) slowly and reflux for 30 min. Cool the reaction mixture in an ice bath and quench with water (1 mL), 5% aqueous sulfuric acid (5 mL), and then dilute with diethyl ether (10 mL). Separate the layers and extract the aqueous layer with diethyl ether (2 x 20mL). Wash the combined extract with 5% aqueous sulfuric acid, aqueous saturated sodium bicarbonate, aqueous saturated ammonium chloride, saturated aqueous sodium chloride, dry (magnesium sulfate), and concentrate the filtrate to one half volume. Add sodium hydride (0.44 g, 11.0 mmol, 60% dispersion in mineral oil) to the solution with cooling and stir at RT overnight. Concentrate and dry the residue in vacuum to give the title product

** Sodium cyclopentylthiolate is prepared from cyclopentyl mercaptan by reaction with 0.95 equivalent of sodium hydride in THF.

Preparation 56

2-(Propane-2-sulfonyl)-6-prop-2-ynylamino-isonicotinic acid

2-Chloro-6-isopropanesulfonyl-isonicotinic acid methyl ester

Add 3-chloroperbenzoic acid (5.32 g, 30.8 mmol) to a solution of 2-chloro-6-isopropylsulfonyl-isonicotinic acid methyl ester (2.37g, 9.63 mmol) in dichloromethane (50 mL) at 0 °C. Stir the mixture at RT for 4 h. Partition the mixture between dichloromethane and aqueous saturated sodium bicarbonate. Extract the aqueous layer with dichloromethane (2 x 50 mL) and wash the combined extracts with water, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 25:75 ethyl acetate:hexanes) to give the title product as a white solid (1.26 g, 47%).

2-(Propane-2-sulfonyl)-6-prop-2-ynylamino-isonicotinic acid methyl ester

Add THF (10 mL), 2-chloro-6-iso-propanesulfonyl-isonicotinic acid methyl ester (0.50 g, 1.80 mmol), N,N-diisopropylethylamine (0.470 mL, 2.70 mmol), and propargylamine (0.740 mL, 10.8 mmol) to a sealed vessel flushed with nitrogen. Heat and stir the reaction at 80 °C overnight. Cool to RT, concentrate and purify (silica gel chromatography, eluting with 20:80 to 30:70 ethyl acetate:hexanes) to give the title product (0.102 g, 19%).

MS (ES): *m/z* =297 [M+H].

2-(Propane-2-sulfonyl)-6-prop-2-ynylamino-isonicotinic acid

Add 1 N lithium hydroxide (0.52 mL, 0.52 mmol) to a solution of 2-(propane-2-sulfonyl)-6-prop-2-ynylamino-isonicotinic acid methyl ester (0.102 g, 0.344 mmol) in THF (2 mL) at 0 °C. Stir the mixture at RT for 3 h and acidify the solution to about pH = 2 and concentrate the solvent to one half volume. Partition the residue between ethyl acetate and water, and extract the aqueous layer with ethyl acetate (2 x 10 mL). Wash the combined organic extract with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (85%).

MS (ES): m/z = 283 [M+H].

The compounds of Preparation 57-59 may be prepared essentially as described in Preparation 53.

Prep	Compound	MS (ES) [M+H]
57	2-Cyclopropylamino-6-isopropanelsulfonyl-isonicotinic acid	283
58	2-Cyclopropyl-methylamino-6-isopropanelsulfony-isonicotinic acid	299
59	2-Cyclobutylamino-6-isopropanelsulfonyl-isonicotinic acid	299

Preparation 60

2-Cyclopropylamino-6-cyclopropanesulfonyl-isonicotinic acid

tert-Butyl-2,6-dichloroisonicotinate

Add 2,6-dichloro-isonicotinic acid (2.00 g, 10.4 mmol) in dichloromethane (25 mL) and THF (5 mL) to a flask equipped with a gas condenser. Cool to 0 °C and slowly add concentrated sulfuric acid. Condense isobutylene gas via a condenser filled with dry ice in acetone until total volume of the solution increases by about 20 mL. Stir the mixture at RT overnight and pour into a cold solution of sodium carbonate. Separate the layers and extract the aqueous layer with dichloromethane (2 x 50 mL). Wash the combined organic extract with water, dry (magnesium sulfate) and concentrate to give the title compound (1.02 g, 40%).

2-Chloro-6-cyclopropylsulfonyl-isonicotinic acid tert-butyl ester

Add sodium cyclopropylthiolate (0.554 g, 5.76 mmol (prepared from treatment of isopropanethiol with 0.95 equivalent of sodium hydride) slowly to a solution of tert-butyl 2,6-dichloroisonicotinate (1.30 g, 5.24 mmol) in DMF (5 mL) at 0 °C. Stir at RT and partition the mixture between diethyl ether (20 mL) and water (20 mL) and extract the aqueous layer with diethyl ether (2 x 20 mL). Wash the combined extract with 5% aqueous lithium hydroxide solution, dry (magnesium sulfate) and concentrate to give the title compound as a crude residue which is used directly in the next reaction without further purification.

2-Chloro-6-cyclopropanesulfonyl-isonicotinic acid tert-butyl ester

Add 3-chloroperbenzoic acid (1.66 g, 9.6 mmol) to a solution of 2-chloro-6-cyclopropylsulfonyl-isonicotinic acid tert-butyl ester (0.785g, 2.74 mmol) in dichloromethane (20 mL) at 0 °C. Stir at RT overnight and partition the mixture between dichloromethane and saturated aqueous sodium bicarbonate and extract the aqueous layer with dichloromethane (2 x 20 mL). Wash the combined extract with water, saturated aqueous sodium chloride, dry (magnesium sulfate) and purify (silica gel chromatography, eluting with 15:85 ethyl acetate:hexanes) to give the title compound (0.193 g, 22%).

2-Cyclopropylamino-6-cyclopropanesulfonyl-isonicotinic acid tert-butyl ester

Add 2-chloro-6-cyclopropanesulfonyl-isonicotinic acid tert-butyl ester (0.190 g, 0.607 mmol), palladium acetate (0.020 g, 0.091 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.057 g, 0.091 mmol), cesium carbonate (0.297 g, 0.911 mmol), and (S)-sec-butylamine (0.063 mL, 0.911 mmol) in toluene (5 mL) to a sealed tube flushed with nitrogen. Heat and stir the reaction mixture at 90 °C for 18 h. Cool and filter the mixture through a pad of filtering agent, concentrate and purify (silica gel chromatography, eluting with 20:80 ethyl acetate:hexanes) to give the title compound (0.120 g, 59%).

MS (ES): m/z = 339 [M+H].

2-Cyclopropylamino-6-cyclopropanesulfonyl-isonicotinic acid

Add trifluoroacetic acid (2 mL) to a solution of 2-cyclopropylamino-6-cyclopropanesulfonyl-isonicotinic acid tert-butyl ester (0.120 g, 0.355 mmol) in dichloromethane (2 mL) at 0 °C. Stir the solution at RT for 3 h, concentrate and dry the title compound (0.076 g, 54%).

MS (ES): m/z = 283 [M+H].

Preparation 61

(S)-2-sec-Butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid

(S)-2-sec-Butylamino-6-methane-sulfonylamino-isonicotinic acid methyl ester

Add 2-sec-butylamino-6-chloro-isonicotinic acid methyl ester (500 mg, 2.07 mmol), toluene (10 mL), tris(dibenzylideneacetone)dipalladium(0) (95 mg, 0.104 mmol),

2-(di-tert-butylphosphino)biphenyl (62 mg, 0.207 mmol), and methanesulfonamide sodium salt (363 mg, 3.11 mmol) to a sealed flask flushed with nitrogen. (Prepare methanesulfonamide sodium salt by adding sodium hydride (2.0 g, 50.0 mmol, 60% dispersion in mineral oil) slowly to a solution of methanesulfonamide (5.0 g, 52.6 mmol) and THF (80 mL) at 0 °C.) Stir the mixture at RT overnight. Concentrate and dry the residue under vacuum. Heat and stir the sealed flask at 100 °C for 18 h. Cool to RT, filter through a pad of filtering agent, wash with dichloromethane, concentrate the filtrate and purify (silica gel chromatography, eluting with 20:80 to 25:75 ethyl acetate:hexanes) to give the title compound (475 mg, 76%).

MS (ES): m/z = 302 [M+H].

(S)-2-sec-Butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid methyl ester

Add sodium hydride (47 mg, 1.18 mmol, 60% dispersion in mineral oil) to a solution of (S)-2-sec-butylamino-6-methanesulfonylamino-isonicotinic acid methyl ester (356 mg, 1.18 mmol) in DMF (5 mL) at 0 °C. Stir for 10 min, add iodomethane (0.11 mL, 1.77 mmol) dropwise. Stir the mixture at RT for 2 h, cool and quench the reaction with an ammonium chloride solution. Extract the mixture with ethyl acetate (3 x30 mL) and wash the combined extract with water, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 20:80 ethyl acetate:hexanes) to give the title compound (320 mg, 86%).

MS (ES): m/z = 316 [M+H].

(S)-2-sec-Butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid

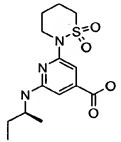
Add 1 N lithium hydroxide (19.5 mL, 19.5 mmol) to a solution of (S)-2-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid methyl ester (2.45 g, 7.77 mmol) in THF (10 mL) at 0 °C. After 2 h at RT, acidify the mixture to about pH = 2 and concentrate. Extract the residue with ethyl acetate (3 x 40 mL), wash the combined extracts with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a yellow solid (2.23 g, 95%).

MS (ES): m/z = 302 [M+H].

The compound of Preparation 62 may be prepared essentially as described in Preparation 61.

Prep	Compound	MS (ES) [M+H]
62	(S)-2-sec-Butylamino-6-methane-sulfonylamino-isonicotinic acid	288

Preparation 63



(S)-2-sec-Butylamino-6-(1,1-dioxo-1λ⁶-[1,2]thiazinan-2-yl)-isonicotinic acid

4-Chlorobutanesulfonyl chloride

Add anhydrous sodium sulfite (16.8 g, 130 mmol) to a solution of 4-chlorobutyl acetate (20.0 g, 133 mmol) in water (50 mL) and reflux the mixture for 20 h. Cool to RT and add concentrated HCl (19.0 mL) and reflux for 1 h. Cool the mixture to RT, neutralize to about pH = 7. Concentrate to about one half the volume, filter away the sodium chloride. Concentrate and dry to give the title compound.

4-Chlorobutanesulfonamide

Chill a suspension of 4-chlorobutanesulfonyl chloride (5.0 g, 26.2 mmol) in dichloromethane (50 mL) and add phosphorous pentachloride (12.0 g, 55.0 mmol) portionwise. Stir the mixture at RT for 4 h and filter away the precipitate. Bubble ammonia gas into the filtrate at 0 °C for 1 h. Stir the mixture for 1 h, filter away the ammonium chloride, concentrate and purify (silica gel chromatography, eluting with 30:70 to 40:60 ethyl acetate:hexanes) to give the title compound (1.18 g, 26%).

[1,2]thiazinane 1, 1-dioxide, sodium salt

Add sodium (0.157 g, 6.84 mmol) to 50 mL of degassed anhydrous ethanol. After dissolution of sodium, add 4-chlorobutanesulfonamide (1.18 g, 6.84 mmol) into the

solution and reflux for 2 h. Cool and filter through a filtering agent, concentrate the filtrate and add ethyl acetate. Filter the mixture through a pad of silica gel and wash with ethyl acetate. Concentrate the filtrate and dry. Convert [1,2]thiazinane 1, 1-dioxide to the title compound by treatment with 0.95 equivalent of sodium hydride in THF, concentrate and dry.

2-sec-Butylamino-6-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-isonicotinic acid methyl ester

Add 2-sec-butylamino-6-chloro-isonicotinic acid methyl ester (1.0 g, 4.13 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.189 g, 0.207 mmol), 2-(di-tert-butylphosphino)biphenyl (0.123 g, 0.413 mmol) and the sodium salt of [1,2]thiazinane 1, 1-dioxide (0.844 g, 5.37 mmol) in toluene (10 mL) to a sealed flask flushed with nitrogen. Heat and stir the sealed flask at 100 °C for 18 h. Cool to RT and filter through a bed of filtering agent, and wash with dichloromethane. Concentrate the filtrate and purify (silica gel chromatography, eluting with 20:80 to 30:70 ethyl acetate:hexanes) to give the title compound (0.533 g, 38%).

MS (ES): m/z = 342 [M+H].

2-sec-Butylamino-6-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-isonicotinic acid

Add 1 N lithium hydroxide (4.0 mL, 3.88 mmol) to a solution of 2-sec-butylamino-6-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-isonicotinic acid methyl ester (0.590 g, 1.80 mmol) in THF (5 mL) at 0 °C. Stir for 2 h at RT and acidify the mixture to about pH = 2 and concentrate. Extract the residue with ethyl acetate (3 x 40 mL) and wash the combined extract with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (0.377 g, 74%).

MS (ES): m/z = 328 [M+H].

The compound of Preparation 64 may be prepared essentially as described in Preparation 63.

Prep	Compound	MS (ES) [M+H]
64	(S)-2-sec-Butylamino-6-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isonicotinic acid	314

Preparation 65

(S)-2-sec-Butylamino-6-dimethylsulfamoyl-isonicotinic acid

2-Benzylsulfanyl-6-chloro-isonicotinic acid methyl ester

Add sodium hydride (0.80 g, 20.0 mmol, 60% dispersion in mineral oil) slowly to a solution of methyl 2,6-dichloroisonicotinate (4.12 g, 20.0 mmol) in DMF at 0 °C. Stir the mixture at RT overnight and partition between diethyl ether (50 mL) and water (50 mL). Extract the aqueous layer with diethyl ether (2 x 30 mL) and wash the combined extract with 5% aqueous lithium hydroxide. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 3:97 ethyl acetate:hexanes) to give the title compound (5.03 g, 86%).

2-Chloro-6-dimethylsulfamoyl-isonicotinic acid methyl ester

Bubble chlorine gas for 30 min into a solution of 2-benzylsulfanyl-6-chloro-isonicotinic acid methyl ester (2.50 g, 8.50 mmol) in water (5 mL) and glacial acetic acid (30 mL) at 0 °C. Concentrate and suspend the residue in THF and add dimethylamine in methanol (2.0 M in methanol, 10.6 mL, 21.2 mmol) with cooling. After stirring at RT overnight, filter through a filtering agent and partition the filtrate between ethyl acetate (50 mL) and water (50 mL). Extract aqueous layer with ethyl acetate (2 x 50 mL) and wash the combined extract with water, saturated aqueous sodium chloride, dry (magnesium sulfate) and filter the filtrate through a pad of silica gel and concentrate to give the title product that is used directly in the next reaction without further purification.

(S)-2-sec-Butylamino-6-dimethylsulfamoyl-isonicotinic acid methyl ester

Add toluene (20 mL), 2-chloro-6-dimethylsulfamoyl-isonicotinic acid methyl ester (2.49 g, 8.93 mmol), palladium acetate (0.201g, 0.893 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.556 g, 0.893 mmol) and cesium carbonate (4.36 g, 13.4 mmol) to a sealed vessel flushed with nitrogen. Slowly add (S)-sec-butylamine (1.36 mL, 13.4 mmol) to the mixture. Heat and stir the sealed vessel at 90 °C overnight. Cool to RT, filter through a pad of filtering agent, concentrate and purify (silica gel chromatography, eluting with 20:80 to 30:70 ethyl acetate:hexanes) to give the title compound (1.43 g, 51%).

MS (ES): $m/z = 326$ [M+H].

(S)-2-sec-Butylamino-6-dimethylsulfamoyl-isonicotinic acid

Add 1 N lithium hydroxide (11.4 mL, 11.4 mmo) to a solution of (S)-2-sec-butylamino-6-dimethylsulfamoyl-isonicotinic acid methyl ester (1.43 g, 4.54 mmol) and THF (10 mL) at 0 °C. Stir the mixture overnight, acidify the solution to about pH = 2 and concentrate solvent to one half volume. Partition the residue between ethyl acetate and water, and extract the aqueous layer with ethyl acetate (2 x 30 mL). Wash the combined organic extract with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): m/z = 302 [M+H].

The compounds of Preparation 66-67 may be prepared essentially as described in Preparation 65.

Prep	Compound	MS (ES) [M+H]
66	(S)-2-sec-Butylamino-6-methylsulfamoyl-isonicotinic acid	288
67	(S)-2-sec-Butylamino-6-(pyrrolidine-1-sulfonyl)-isonicotinic acid	328

Preparation 68

6-Cyclobutylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester

2-Chloro-6-(1-ethoxyvinyl)-isonicotinic acid methyl ester

Add 2,6-dichloro-isonicotinic acid methyl ester, tetrakis(triphenylphosphine)palladium(0) (0.763 g, 0.66 mmol), triphenylphosphine (0.346 g, 1.32 mmol), tributyl(1-ethoxyvinyl)tin (5.0 g, 13.9 mmol) and toluene (30 mL), to a sealed flask flushed with nitrogen. Heat at 100 °C overnight and cool to RT. Filter the mixture through a filtering agent, concentrate and purify (silica gel chromatography eluting with 25:75 ethyl acetate:hexanes) to give the title compound (84%).

6-Chloropyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester

Chill a solution of 2-chloro-6-(1-ethoxyvinyl)-isonicotinic acid methyl ester (2.47 g, 10.2 mmol) in dichloromethane (20 mL) at –78 °C and bubble ozone into it for 15 min until light blue in color. Quench with dimethylsulfide and stir at RT for 3 h. Concentrate

and purify (silica gel chromatography, eluting with 15:85 ethyl acetate:hexanes) to give the title compound (1.44 g, 58%).
MS (ES): *m/z* = 244 [M+H].

6-Cyclobutylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester

Add 6-chloropyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (0.500 g, 2.05 mmol), palladium acetate (0.0461g, 0.205 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.128 g, 0.205 mmol), cesium carbonate (0.801 g, 2.46 mmol) and toluene (5 mL), to a sealed vessel flushed with nitrogen. Slowly add cyclobutylamine (0.210 mL, 2.46 mmol) and heat and stir the sealed vessel at 90 °C overnight. Cool to RT, filter through a pad of filtering agent, concentrate and purify (silica gel chromatography, eluting with 10:90 to 20:80 ethyl acetate:hexanes) to give the title compound (0.223 g, 39%).
MS (ES): *m/z* = 279 [M+H].

6-Cyclobutylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester

Add 1 N lithium hydroxide (0.80 mL, 0.802 mmol) to a solution of 6-cyclobutylaminopyridine-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (0.223 g, 0.802 mmol) in THF (2 mL) at 0 °C. Stir for 1 h, acidify the solution to about pH = 2, concentrate the solvent to one half volume. Partition the residue between ethyl acetate and water, and extract the aqueous layer with ethyl acetate (2 x 15 mL). Wash the combined organic extracts with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound.
MS (ES): *m/z* = 279 [M+H].

Preparation 69

2-sec-Butylamino-6-(propane-1-sulfinyl)-isonicotinic acid

2-sec-Butylamino-6-propylsulfanyl-isonicotinic acid methyl ester

Add 2-chloro-6-propylsulfanyl-isonicotinic acid methyl ester (1.35 g, 5.49 mmol) palladium acetate (0.123 g, 0.549 mmol, 0.1eq.), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.342 g, 0.549 mmol, 0.1eq.), cesium carbonate (2.68 g, 8.24 mmol, 1.5 eq.) and toluene (20 mL) into a sealed vessel flushed with nitrogen. Slowly add (S)-sec-

butylamine (0.824 mL, 8.24 mmol) and heat and stir the reaction mixture at 90 °C for 18 h. Cool the reaction mixture to RT, dilute with ether and filter through a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with the 5:95 to 10:90 ethyl acetate:hexanes) to give the title compound (55%).

MS (ES): m/z = 284 [M+H].

(S)-2-sec-Butylamino-6-(propane-1-sulfinyl)-isonicotinic acid methyl ester

Add sodium perborate monohydrate (0.133 g, 1.33 mmol) to a cooled solution of (S)-2-sec-butylamino-6-propylsulfanyl-isonicotinic acid methyl ester (0.396 g, 1.40 mmol) in acetic acid (4 mL). Stir at RT overnight and concentrate. Dissolve the residue in ethyl acetate and wash the solution with aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 30:70 ethyl acetate:hexanes) to give the title compound (0.230 g, 55 %).

(S)-2-sec-Butylamino-6-(propane-1-sulfinyl)-isonicotinic acid

Add 1 N lithium hydroxide (1.15 mL, 1.15 mmol) to a solution of (S)-2-sec-butylamino-6-(propane-1-sulfinyl)-isonicotinic acid methyl ester (0.229 g, 0.767 mmol) in THF (2 mL) at 0 °C. Stir at RT for 3 h, acidify the solution to about pH = 2 and concentrate to one half of the solvent. Partition the residue between ethyl acetate and water. Extract the aqueous layer with ethyl acetate (2 x 10 mL). Wash the combine organic extract with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (95%).

MS (ES): m/z = 283 [M-H].

The compound of Preparation 70 may be prepared essentially as described in Preparation 69 using sodium thiomethoxide with 3-chloroperbenzoic acid as the oxidant.

Prep	Compound	MS (ES) [M+H]
70	(S)-2-sec-Butylamino-6-(methane-1-sulfinyl)-isonicotinic acid	257

Preparation 71

(S)-2-sec-Butylamino-6-(2-fluorophenyl)-isonicotinic acid

(S)-2-sec-Butylamino-6-(2-fluorophenyl)-isonicotinic acid methyl ester

Add (S)-2-sec-butylamino-6-chloroisonicotinic acid methyl ester (1.40 g, 5.75 mmol), 2-fluorophenylboronic acid (1.0 g, 7.15 mmol), tetrakis(triphenylphosphine)palladium (0) (0.664 g, 0.575 mmol), potassium carbonate (2.38 g, 17.3 mmol) and 1,4-dioxane (25 mL) to a sealed flask flushed with nitrogen. Heat and stir the mixture overnight and cool to RT. Filter the mixture through a filtering agent, concentrate and purify (silica gel chromatography, eluting with 4:96 ethyl acetate:hexanes) to give the title compound (1.31 g, 75%).

MS (ES): $m/z = 303$ [M+H].

(S)-2-sec-Butylamino-6-(2-fluorophenyl)-isonicotinic acid

Chill a solution of (S)-2-sec-butylamino-6-(2-fluorophenyl)-isonicotinic acid methyl ester (1.31 g, 4.32 mmol) in methanol (5 mL) and THF (5 mL). Add 2 N NaOH (6.50 mL, 13.0 mmol) stir at RT for 3 h, and acidify the solution to about pH = 2 and concentrate to one half of the solvent. Partition the residue between ethyl acetate and water. Extract the aqueous layer with ethyl acetate (2 x 30 mL). Wash the combined organic extracts with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (80%).

MS (ES): m/z = 289 [M+H].

Preparation 72

2-Cyclopropylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid

2-Chloro-6-methane-sulfonylamino-isonicotinic acid methyl ester

Add methyl 2, 6-dichloro-isonicotinate (2.06 g, 10.0 mmol), toluene (10 mL), tris(dibenzylideneacetone)dipalladium(0) (0.458 g, 0.50 mmol), 2-(di-tert-butylphosphino)biphenyl (0.298 g, 1.00 mmol), and methanesulfonamide sodium salt (1.17 g, 10.0 mmol) to a sealed flask flushed with nitrogen. Heat and stir the sealed flask at 100 °C for 18 h. Cool the mixture to RT and filter through a pad of filtering agent, and wash the solid with dichloromethane. Concentrate and purify (silica gel chromatography, eluting with 20:80 to 30:70 ethyl acetate:hexanes) to give the title compound (1.31g, 50%).

2-Chloro-6-(methanesulfonyl-methylamino)-isonicotinic acid methyl ester

Add sodium hydride (257 mg, 6.43 mmol, 60% dispersion in mineral oil) at 0 ° C to a solution of 2-chloro-6-methanesulfonylamino-isonicotinic acid methyl ester (1.31 g, 4.95 mmol) in DMF (10 mL). After stirring at 0 ° C for 15 min, add iodomethane (0.4 mL, 6.43 mmol). Stir the reaction at 0° C for 1 h and at RT for 2 h. Quench the reaction with ice and extract the reaction mixture with ethyl acetate. Wash the organic layer with saturated aqueous sodium chloride, dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 30:70 ethyl acetate:hexanes) to give the title compound (1.0 g,72%).

2-Cyclopropylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid methylester

Add palladium acetate (29 mg, 0.13 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (81 mg, 0.13 mmol), cesium carbonate (531 mg, 1.63 mmol), toluene (10 mL), and 2-chloro-6-(methanesulfonyl-methylamino)-isonicotinic acid methyl ester (347 mg, 1.25 mmol) to a sealed tube. After degassing the reaction vessel with nitrogen, add cyclopropylamine (0.114 mL, 1.63 mmol) to the reaction mixture. Heat the reaction vessel at 90° C overnight. Cool to RT and filter the solids through a filtering agent. Wash with ethyl acetate. Concentrate the combined filtrates and purify (silica gel chromatography, eluting with 30:70 ethyl acetate:hexanes) to give the title compound (261 mg 70%).

2-Cyclopropylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid

Treat a solution of 2-cyclopropylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid methyl ester (261 mg, 0.87 mmol) in methanol (8 mL) with 1 N NaOH (1.3 mL, 1.31 mmol) at RT. Stir for 5 h, acidify with 1 N HCl to about pH = 3. Extract the reaction mixture with ethyl acetate, dry (sodium sulfate) and concentrate to give the title compound (226 mg, 91%).

MS (ES): m/z = 286 [M+H].

Preparation 73

(S)-2-sec-Butylamino-6-(2H-tetrazol-5-yl)-isonicotinic acid

(S)-2-sec-Butylamino-6-cyano-isonicotinic acid methyl ester

Add 2-sec-butylamino-6-chloro-isonicotinic acid methyl ester (1.22 g, 5.0 mmol), tris(dibenzylideneacetone)dipalladium (183 mg, 0.2 mmol), 1,1'-bis(diphenylphosphino)ferrocene (222 mg, 0.4 mmol), zinc cyanide (587 mg, 5.0 mmol), and zinc dust (78 mg, 1.2 mmol) in N,N-dimethylacetamide (10 mL) and heat in a sealed tube at 120 °C overnight. Cool to RT, filter through a filtering agent, concentrate and purify (silica gel chromatography, eluting with 10:90 to 15:85 ethyl acetate:hexanes) to give the title compound (703 mg, 59%).

MS (ES): m/z = 234 [M+H].

(S)-2-sec-Butylamino-6-(2H-tetrazol-5-yl)-isonicotinic acid methyl ester

Heat a suspension of (S)-2-sec-butylamino-6-cyano-isonicotinic acid methyl ester (932 mg, 4.0 mmol), sodium azide (780 mg, 12 mmol), and triethylamine hydrochloride (1.65 g, 12 mmol) in toluene (13 mL) at 90 °C for 2 days. Cool to RT and extract with water (3 x 30 mL), acidify the combined aqueous layers to about pH = 2 using 1 N HCl, extract the desired product with ethyl acetate (4 x 50 mL), dry (sodium sulfate) and concentrate to give the title compound (720 mg, 65%).

MS (ES): m/z = 277 [M+H].

(S)-2-sec-Butylamino-6-(2H-tetrazol-5-yl)-isonicotinic acid

Treat a solution of (S)-2-sec-butylamino-6-(2H-tetrazol-5-yl)-isonicotinic acid methyl ester (250 mg, 0.91 mmol) in methanol (4 mL)at RT with 2 N NaOH (1.36 mL, 2.72 mmol). Stir overnight, acidify with 1 N HCl to about pH = 3, concentrate and lyophilize to give the title compound.

MS (ES): m/z = 261 [M-H].

Preparation 74

(S)-2-sec-Butylamino-6-(2-ethyl-2H-tetrazol-5-yl)-isonicotinic acid

(S)-2-sec-Butylamino-6-(1-ethyl-1H-tetrazol-5-yl)-isonicotinic acid

(S)-2-sec-Butylamino-6-(2-ethyl-2H-tetrazol-5-yl)-isonicotinic acid methyl ester

(S)-2-sec-Butylamino-6-(1-ethyl-1H-tetrazol-5-yl)-isonicotinic acid methyl ester

Treat a solution of (S)-2-sec-butylamino-6-(2H-tetrazol-5-yl)-isonicotinic acid methyl ester (720 mg, 2.61 mmol) in DMF (10 mL) with potassium carbonate (541 mg, 3.92 mmol) and iodoethane (0.364 mL, 3.92 mL) at RT. Dilute with ethyl acetate (100 mL), wash with water (twice), saturated aqueous sodium chloride, dry (sodium sulfate) and concentrate to give approximately a 1:1 mixture of the two title compounds which are used directly in the next step without further purification.

MS (ES): m/z = 303 [M-H].

(S)-2-sec-Butylamino-6-(2-ethyl-2H-tetrazol-5-yl)-isonicotinic acid

(S)-2-sec-Butylamino-6-(1-ethyl-1H-tetrazol-5-yl)-isonicotinic acid

Dissolve the crude product mixture of (S)-2-sec-butylamino-6-(2-ethyl-2H-tetrazol-5-yl)-isonicotinic acid methyl ester and (S)-2-sec-butylamino-6-(1-ethyl-1H-tetrazol-5-yl)-isonicotinic acid methyl ester (approximately 2.61 mmol) in methanol (10 mL) and treat with 2 N NaOH (1.95 mL, 3.9 mmol) overnight. Acidify the reaction mixture to about pH = 3 and extract with ethyl acetate (3 x 50 mL). Dry (sodium sulfate), and concentrate to give the title compounds as a crude mixture.

MS (ES): *m/z* = 289 [M-H].

Preparation 75

(S)-2-sec-Butylamino-6-(2-methyl-2H-tetrazol-5-yl)-isonicotinic acid

(S)-2-sec-Butylamino-6-(2-methyl-2H-tetrazol-5-yl)-isonicotinic acid methyl ester

Treat a solution of (S)-2-sec-butylamino-6-(2H-tetrazol-5-yl)-isonicotinic acid methyl ester (350 mg, 1.26 mmol) in ethyl acetate (8 mL) with trimethyloxonium tetrafluoroborate at RT for 3 h. Dilute with ethyl acetate (50 mL) and wash with saturated sodium bicarbonate and saturated aqueous sodium chloride. Dry (sodium sulfate) and concentrate to give the title compound which is used directly in the next step without further purification.

MS (ES): *m/z* = 291 [M+H].

(S)-2-sec-Butylamino-6-(2-methyl-2H-tetrazol-5-yl)-isonicotinic acid

Treat a solution of (S)-2-sec-butylamino-6-(2-methyl-2H-tetrazol-5-yl)-isonicotinic acid methyl ester (250 mg, 0.86 mmol) in methanol (5 mL) with 2 N NaOH (0.64 mL, 1.29 mmol). Stir at RT overnight, acidify the reaction to about pH = 3 using 1 N HCl. Extract the reaction mixture with ethyl acetate (3 x 25 mL). Wash the combined organic layers with saturated aqueous sodium chloride, dry (sodium sulfate) and concentrate to give the title compound.

MS (ES): *m/z* = 277 [M+H].

Preparation 76

(S)-2-sec-Butylamino-isonicotinic acid

(S)-2-sec-Butylamino-isonicotinic acid methyl ester

Degas with nitrogen a suspension containing 2-chloro-isonicotinic acid methyl ester (2.15 g, 12.5 mmol), palladium acetate (281 mg, 1.25 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (780 mg, 1.25 mmol), cesium carbonate (4.95 g, 15 mmol), and (S)-sec-butylamine (1.5 mL, 15 mmol) in toluene (30 mL) and heat in a sealed tube at 90 °C overnight. Cool to RT and filter the solids through a filtering agent. Wash with ethyl acetate (30 mL), concentrate and purify (silica gel chromatography, eluting with 15:85 to 30:70 ethyl acetate:hexanes) to give the title compound.

(S)-2-sec-Butylamino-isonicotinic acid

Treat a solution of (S)-2-sec-butylamino-isonicotinic acid methyl ester (2.69 g, 12.5 mmol) in methanol (35 mL) with 1 N NaOH (15 mL, 15 mmol) at RT for 5 hr. Acidify to about pH = 3 with 1 N HCl. Concentrate and redissolve the residue in a 1:1 CH_3CN:water solution and lyophilize to give the title compound.
MS (ES): m/z = 193 [M-H].

Preparation 77

(S)-2-sec-Butylamino-6-difluoromethoxy-isonicotinic acid

2-Chloro-6-methoxy-isonicotinic acid ethyl ester

Treat an ethanol suspension of 2-chloro-6-methoxy-isonicotinic acid (3.75 g, 20 mmol) at 0 °C with thionyl chloride for 30 min. Heat at 70 °C overnight. Cool to RT, concentrate, dissolve the residue in ethyl acetate (200 mL), wash the organic layer with saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, dry (magnesium sulfate) and concentrate to give the title compound (4.2 g, 98%).

(S)-2-sec-Butylamino-6-methoxy-isonicotinic acid ethyl ester

Add (S)-sec-butyl amine (1.18mL, 11.8mmol) to a suspension of 2-chloro-6-methoxy-isonicotinic acid ethyl ester (1.69g, 7.86mmol), palladium acetate (0.088g, 0.4mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.250g, 0.4mmol), and

cesium carbonate (3.8g, 11.8mmol) in toluene (20 mL) at RT and stir 15 h at 80 °C. Cool to RT, filter through a filtering agent, concentrate and purify (silica gel chromatography, eluting with 5:95 ethyl acetate:hexanes to give the title compound (1.85 g, 93%).
MS (ES): m/z = 253 [M+H].

(S)-2-sec-Butylamino-6-hydroxy-isonicotinic acid ethyl ester

Treat sodium iodide (5.58g, 36.7mmol) and (S)-2-sec-butylamino-6-methoxy-isonicotinic acid ethyl ester (1.85g, 7.3mmol) in acetonitrile (30 mL) with chlorotrimethylsilane (4.66 mL, 36.7 mmol) and stir at reflux for 38 h. Quench with methanol (10 mL), stir for 24 h, and concentrate. Dissolve residue in ethyl acetate, wash with water, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 70:30 to 100:0 ethyl acetate:hexanes) to give the title compound (0.98 g, 56%).
MS (ES): m/z = 239 [M+H].

(S)-2-sec-Butylamino-6-difluoromethoxy-isonicotinic acid ethyl ester

Add cesium carbonate (0.352g, 1.08mmol) to (S)-2-sec-butylamino-6-hydroxy-isonicotinic acid ethyl ester (0.172g, 0.72mmol) in butan-2-one (10 mL) ((Bioorg. Med. Chem. Lett., 12, 2149-2152 (2002)). Heat at 70 °C for 30 min and add chlorodifluoroacetic acid methyl ester (0.24 mL, 2.16mmol) in three equal portions over 3 h. Heat for 3 days at 70 °C. Add again chlorodifluoroacetic acid methyl ester (0.24 mL, 2.16mmol) in three equal portions over 3 h and stir at RT for 24 h. Concentrate and dissolve the crude mixture in ethyl acetate and filter. Purify (silica gel chromatography, eluting with 2:98 to 6:92 ethyl acetate:hexanes) to give the title compound (0.135g, 65%).
MS (ES): m/z = 289 [M+H].

(S)-2-sec-Butylamino-6-difluoromethoxy-isonicotinic acid

Add 2 N NaOH (0.67 mL) to (S)-2-sec-butylamino-6-difluoromethoxy-isonicotinic acid ethyl ester in ethanol (5 mL). Stir 3 h and acidify to about pH = 4 with 1 N HCl and extract with ethyl acetate. Wash organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (0.1 g, 85%).

MS (ES): $m/z = 261$ [M+H].

Preparation 78

2-Methanesulfonyl-6-(methylpropylamino)-isonicotinic acid

2-Chloro-6-methanesulfonyl-isonicotinic acid methyl ester

Stir a mixture of 2,6-dichloro-isonicotinic acid methyl ester (20 g, 90.0 mmol) and sodium methyl thiolate (6.4 g, 90.9 mmol) in DMF (90 mL overnight at RT. Partition the reaction between of diethyl ether (50 mL) and water (100 mL). Extract the organics with diethyl ether (2 x 25 mL). Wash the combined organic layers with 5% aqueous lithium chloride solution, dry (magnesium sulfate) and concentrate to give an oil (19.12 g). Dissolve in dichloromethane (100 mL) and cool the solution in a wet ice/acetone bath. Add peracetic acid (15 mL) dropwise. Remove the ice bath and stir overnight. Quench the reaction with water (100 mL) and solid sodium bisulfite to a negative starch iodide endpoint. Separate the organic layer, dry (magnesium sulfate) and concentrate. Crystallize by the addition of hexanes to give a white solid. Filter the slurry, wash with hexanes, and dry under vacuum to give the title compound (13.7 g) as a white crystalline solid. Recover a second crop of the title compound (6 g) from the filtrate (19.7 g, 83% total yield).

2-Methanesulfonyl-6-(methylpropylamino)-isonicotinic acid methyl ester

Add methylpropylamine (0.21 mL, 2.0 mmol) to a suspension of 2-chloro-6-methanesulfonyl-isonicotinic acid methyl ester (0.25 g, 1.0 mmol), palladium acetate (0.022 g, 0.1mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.062 g, 0.1 mmol), and cesium carbonate (0.325 g, 1.0 mmol) in toluene (5 mL) at RT and stir 18 h at 80 °C. Cool, filter through a filtering agent and purify (silica gel chromatography, eluting with 20:80 to 40:60 ethyl acetate:hexanes) to give the title compound (0.181g, 63%).

2-Methanesulfonyl-6-(methylpropylamino)-isonicotinic acid

Add 2 N NaOH (0.95 mL) to 2-methanesulfonyl-6-(methylpropylamino)-isonicotinic acid methyl ester (0.181 g, 0.63 mmol) in methanol (5 mL). Stir 3 h, acidify to about pH = 3 using 1 N HCl, extract into ethyl acetate, wash organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (0.14g, 85%).

MS (ES): *m/z* = 273 [M+H].

Preparation 79

2-Cyclobutylamino-6-methanesulfonyl-isonicotinic acid

2-Cyclobutylamino-6-methanesulfonyl-isonicotinic acid methyl ester

Add cyclobutylamine (0.13 mL, 1.5 mmol) to a suspension of 2-chloro-6-methanesulfonyl-isonicotinic acid methyl ester (0.25 g, 1.0 mmol), palladium acetate (0.022 g, 0.1 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.062 g, 0.1 mmol), and cesium carbonate (0.325 g, 1.0 mmol) in toluene (5 mL) at RT and heat for 16 h at 80 °C. Cool, filter through a filtering agent, concentrate and purify (silica gel chromatography, eluting with 15:85 to40:60 ethyl acetate:hexanes) to give the title compound (0.255 g, 90%).

2-Cyclobutylamino-6-methanesulfonyl-isonicotinic acid

Add 2 N NaOH (1.26 mL) to 2-cyclobutylamino-6-methanesulfonyl-isonicotinic acid methyl ester (0.24 g 0.85 mmol) in methanol (5 mL). Stir 3 h, acidify to about pH = 3 with 1 N HCl, extract into ethyl acetate, wash organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (0.19g, 86%).

MS (ES): *m/z* = 271 [M+H].

The compounds of Preparation 80-81 may be prepared essentially as described in Preparation 79 using the appropriate amine.

Prep	Compound	MS (ES) [M+H]
80	2-Pyrrolidin-1-yl-6-methanesulfonyl-isonicotinic acid	271

81	2-Cyclopropylamino-6-methanesulfonyl-isonicotinic acid	

Preparation 82

2-(Methanesulfonyl-methylamino)-6-(methylpropylamino)-isonicotinic acid

2-Chloro-6-(methylpropylamino)-isonicotinic acid methyl ester

Mix 2,6-dichloro-isonicotinic acid methyl ester (5 g, 24.2 mmol), methylpropylamine (3.2 g, 23.06mmol), cesium carbonate (10 g, 31.2 mmol), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.5 g, 2.43 mmol), and palladium acetate (0.27 g, 1.21 mmol) in toluene (50 mL). Degas with argon, seal the vessel and heat at 80 °C for 16 h. Cool to RT and dilute with diethyl ether (50 mL). Filter through a filtering agent, concentrate, and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes to give the title compound as an oil (795 mg, 13.5%).
^{1}H NMR ($CDCl_3$) δ 7.00 (s, 1 H), 6.93 (s, 1 H), 3.92 (s, 3 H), 3.49 (t, J = 7.2 Hz, 2 H), 3.09 (s, 3 H), 1.69-1.59 (m, 2 H), 0.94 (t, J = 7.6 Hz, 3 H).

2-Methanesulfonylamino-6-(methylpropylamino)-isonicotinic acid methyl ester

Dissolve methane sulfonamide (951 mg, 10 mmol) in THF (30 mL). Add sodium hydride (380 mg, 9.5mmol, 60% dispersion in mineral oil) and reflux for 3 h, cool to RT and concentrate. Charge a sealed flask with sodium methansulfonamide (478 mg, 4.09 mmol), 2-chloro-6-(methylpropylamino)-isonicotinic acid methyl ester (79mg, 3.27 mmol), biphenyl-2-yl-di-tert-butylphosphane (98 mg, 0.33 mmol), and tris(dibenzylideneacetone)dipalladium (0) (150 mg, 0.16mmol) in toluene (7 mL). Degas with argon, seal the vessel and heat at 100 °C for 16 h. Cool to RT, dilute with ethyl acetate, wash with water, aqueous sodium chloride, concentrate and purify (silica gel chromatography, eluting with 0:100 to 50:50 ethyl acetate:hexanes) to give the title compound as an oil (870 mg, 88%).
MS (ES): m/z = 302 [M+H].

2-(methanesulfonyl-methylamino)-6-(methylpropylamino)-isonicotinic acid methyl ester

Dissolve 2-methanesulfonylamino-6-(methylpropylamino)-isonicotinic acid methyl ester (87mg, 2.89 mmol) and iodomethane (0.27 mL, 4.33 mmoles) in DMF (10 mL). Add potassium carbonate (639 mg, 4.62 mmol) and tetrabutylammonium bromide

(93 mg, 0.98 mmol) and stir at RT 1 h. Dilute with ethyl acetate (80 mL), wash with 10% aqueous potassium carbonate (2 x 15 mL), 0.1 N citric acid (2 x 15 mL), 1 N lithium chloride (2 x 15 mL) and saturated aqueous sodium chloride (15 mL). Concentrate organic layer and purify (silica gel chromatography, eluting with 10:90 to 40:60 ethyl acetate:hexanes to give the title compound (796 mg, 87%).
MS (ES): m/z = 316 [M+H].

2-(methanesulfonyl-methylamino)-6-(methylpropylamino)-isonicotinic acid

Dissolve 2-(methanesulfonyl-methylamino)-6-(methylpropylamino)-isonicotinic acid methyl ester (796 mg, 2.52 mmoles) in THF (35 mL) and add 1 N lithium hydroxide (12.6 mL). Stir at RT for 16 h, acidify with 5 N HCl (2.6mL), and partition between diethyl ether and water. Wash the diethyl ether layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a yellow solid (650 mg, 85%).
MS (ES): m/z = 302 [M+H].

Preparation 83

2-Benzenesulfonyl-6-(S)-sec-butylamino)-isonicotinic acid

2-benzenesulfonyl-6-chloro-isonicotinic acid methyl ester

Mix 2,6-dichloro-isonicotinic acid methyl ester (1 g, 4.85 mmol) and sodium thiophenoxide (0.64 g, 4.85 mmol) in DMF (10 mL) at RT for 4 h. Quench with water and extract with dichloromethane. Dry the dichloromethane layer over magnesium sulfate and concentrate. Dissolve the residue in chloroform (30 mL) and add neutral alumina (6 g) and potassium peroxymonosulfate (11.92 g, 19.39 mmol). Reflux for 16 h, concentrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the title compound as a white solid (1.4 g, 93%).
MS (ES): m/z = 312 [M+H].

2-Benzenesulfonyl-6-(S)-sec-butylamino)-isonicotinic acid

In a sealed tube mix 2-benzenesulfonyl-6-chloro-isonicotinic acid methyl ester (1.4 g, 4.49 mmol), palladium acetate (0.1 g, 0.45 mmol), cesium carbonate (2.19 g, 6.74 mmol), (S)-sec-butylamine (0.36 g, 4.94 mmoles) and racemic 2,2'-

bis(diphenylphosphino)-1,1'-binaphthyl (0.28 g, 0.45 mmol) in toluene (50 mL). Degas with argon, seal the flask and heat at 80 °C for 16 h. Cool to RT and partition between diethyl ether and water. Dry the organic layer over magnesium sulfate, concentrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the methyl ester (490mg, 31%) as an oil. Dissolve the oil in THF (14 mL) and add 1 N lithium hydroxide (7 mL). Stir vigorously at RT for 4 h and concentrate. Partition the residue between diethyl ether and 1 N HCl, dry the organic layer (magnesium sulfate) and concentrate to give the title compound as a white solid (430 mg, 91%).

MS (ES): m/z = 335 [M+H].

Preparation 84

2-sec-Butylamino-6-methanesulfonyloxy-isonicotinic acid

2-Benzyloxy-6-chloro-isonicotinic acid methyl ester

Add sodium hydride (1.15 g, 28.75 mmol 60% in mineral oil) to a suspension of 2,6-dichloroisonicotinic acid (2 g, 10.42 mmol) at 0 °C in DMF (40 mL). Warm to RT and stir for 10 min. Add benzyl alcohol (1.35 mL, 13.045 mmol) dropwise and heat to 80 °C for 1 h. Cool to RT, add diiodomethane (2 mL) and stir for 30 min. Pour into saturated aqueous sodium chloride and partition between ethyl acetate and water. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 5:95 ethyl acetate:hexanes) to give the title compound as a colorless oil (2.3 g, 79%).

MS (ES): m/z = 278 [M+H].

2-Benzyloxy-6-sec-butylamino-isonicotinic acid methyl ester

Degas a sealed tube for 5 min and add a suspension 2-benzyloxy-6-chloro-isonicotinic acid methyl ester (1 g, 3.604 mmol), palladium acetate (100 mg, 0.445 mmol), racemic 2,2'-bis-diphenylphosphanyl-[1,1']binaphthalenyl (307 mg, 0.493 mmol), cesium carbonate (1.2 g, 3.683 mmol) and (R)-sec-butylamine (0.5 mL, 1.387 mmol) in toluene (14 mL). Heat to 105 °C and stir for 20 h. Cool to RT, concentrate and purify (silica gel chromatography, eluting with 3:97 ethyl acetate:hexanes) to give the title compound.

MS (ES): m/z = 315 [M+H].

2-sec-Butylamino-6-hydroxy-isonicotinic acid

Treat a solution of 2-benzyloxy-6-sec-butylamino-isonicotinic acid methyl ester (340 mg, 1.036 mmol) in methanol (15 mL) and ethyl acetate (5 mL) with 10% Pd/C (150 mg). Stir the mixture under a balloon containing hydrogen gas for 2.5 h. Filter through a filtering agent, wash with ethyl acetate and concentrate to give the title compound which is used directly in the next step without further purification.
MS (ES): m/z = 225 [M+H].

2-sec-Butylamino-6-methanesulfonyloxy-isonicotinic acid methyl ester

Add methanesulfonyl chloride (0.1 mL, 1.292 mmol) to a solution of 2-sec-butylamino-6-hydroxy-isonicotinic acid (242 mg, 1.016 mmol) and triethyl amine (0.25 mL, 1.793 mmol) in dichloromethane (15 mL) at 0 °C. Stir at RT for 15 min, dilute with dichloromethane, wash with saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 15:85 ethyl acetate:hexanes) to give the title compound as a white solid (240 mg, 75%).
MS (ES): m/z = 303 [M+H].

2-sec-Butylamino-6-methanesulfonyloxy-isonicotinic acid

Add 1 N lithium hydroxide (2 mL) to a solution of 2-sec-butylamino-6-methanesulfonyloxy-isonicotinic acid methyl ester (235 mg, 0.743 mmol) in THF (15 mL) at 0 °C. Warm to RT and stir for 12 h. Acidify with 5% aqueous HCl to about pH = 3, extract with ethyl acetate, dry (magnesium sulfate), and concentrate to give the title compound.
MS (ES): m/z = 289 [M+H].

Preparation 85

6-Fluoro-N,N-dipropyl-isophthalamic acid

3-Bromo-4-fluoro-N,N-dipropylbenzamide

Combine 3-bromo-4-fluorobenzoic acid (5.0 g, 22.8 mmol) with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (4.4 g, 22.8 mmol) and N-hydroxy-succinimide (2.6 g, 22.8 mmol) in dichloromethane (75 mL) and stir at RT for 30 min. Add N,N-dipropylamine (4.7 mL, 34.3 mmol) and triethylamine (8.0 mL, 57.1 mol) and

stir at RT overnight. Dilute with ethyl acetate and wash with 1 N HCl, saturated aqueous potassium carbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 30:70 ethyl acetate:hexanes) to give the title compound.

^{1}HNMR ($CDCl_3$) δ 0.79-0.99 (m, 6H), 1.56-1.68 (m, 4H), 3.17-3.44 (m, 4H), 7.14 (t, 1H)), 7.26-7.31 (m, 1H)), 7.56-7.58 (m, 1H).

3-Cyano-4-fluoro-N,N-dipropylbenzamide

Combine 3-bromo-4-fluoro-N,N-dipropylbenzamide (1.0 g, 3.3 mmol) with copper cyanide (0.45 g, 5.0 mmol) in DMF (5 mL) and heat at reflux until all starting material is consumed. Cool to RT and partition between ethyl acetate and saturated aqueous sodium bicarbonate. Separate the organic layer and wash with saturated aqueous sodium bicarbonate, saturated sodium chloride solution, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 20:80 ethyl acetate:hexanes) to give the title compound.

^{1}HNMR ($CDCl_3$) δ 0.79-0.99 (m, 6H), 1.66-1.69 (m, 4H)), 3.15-3.45 (m, 4H)), 7.27 (t, 1H), 7.60-7.65 (m, 2H).

6-Fluoro-N,N-dipropyl-isophthalamic acid

Dissolve 3-cyano-4-fluoro-N,N-dipropylbenzamide (0.52 g, 2.1 mmol) in a 3:1 solution of concentrated sulfuric acid:water (5 mL). Heat at 150 °C until no starting material remains. Cool to RT, pour into water and extract with ethyl acetate. Wash the organic layer with saturated aqueous sodium chloride solution, dry (magnesium sulfate) and concentrate to give the title compound that is used without further purification.

MS (ES): *m/z* 268.0 = [M+H].

Preparation 86

5-(Methyl-propylcarbamoyl)-isophthalic acid monoethyl ester

5-(Methyl-propylcarbamoyl)-isophthalic acid diethyl ester

Stir a solution of diethyl 1,3,5-benzene tricarboxylate (2.47 g, 9.28 mmol), 1-hydroxybenzotriazole (1.38 g, 10.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.96 g, 10.2 mmol), N-methylpropylamine (1.04 mL,

10.2 mmol) in dichloromethane (50 mL) at RT overnight. Dilute with dichloromethane (300 mL) and extract the solution with 0.1 N citric acid (2 x 50 mL), saturated aqueous sodium bicarbonate (50 mL), and saturated aqueous sodium chloride (50 mL). Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound (2.02 g, 68%).
MS (ES): $m/z = 322$ [M+H].

5-(Methyl-propylcarbamoyl)-isophthalic acid monoethyl ester

Stir a solution of 5-(methyl-propylcarbamoyl)-isophthalic acid diethyl ester (2.02 g, 6.3 mmol), NaOH (0.25 g, 6.3 mmol) and ethanol (32 mL) at RT overnight. Add 0.2 N HCl (60 mL) and extract with ethyl acetate (2 x 50 mL). Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes with 1% acetic acid then 100% ethyl acetate with 1% acetic acid) to give the title compound as an oil (1.4 g, 75%).
MS (ES): $m/z = 294$ [M+H].

Preparation 87

3-Ethylcarbamoyl-5-(methyl-propylcarbamoyl)-benzoic acid

3-Ethylcarbamoyl-5-(methyl-propylcarbamoyl)-benzoic acid ethyl ester

Stir a solution of 5-(methyl-propylcarbamoyl)-isophthalic acid monoethyl ester (146 mg, 0.5 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (110 mg, 0.55 mmol), ethylamine (2 N in THF, 0.275 mL, 0.55 mmol) in 0.75 mL DMF at RT overnight. Dilute with dichloromethane (15 mL) and wash with water (5 mL), 0.1 N aqueous citric acid (5 mL), saturated aqueous sodium bicarbonate (5 mL), and saturated aqueous sodium chloride (5 mL). Dry (magnesium sulfate) and concentrate to give the title compound (157 mg, 100%).
MS (ES): $m/z = 321$ [M+H].

3-Ethylcarbamoyl-5-(methyl-propylcarbamoyl)-benzoic acid

Stir a solution of 3-ethylcarbamoyl-5-(methyl-propylcarbamoyl)-benzoic acid ethyl ester (157 mg, 0.5 mmol), 1 N aqueous lithium hydroxide (2.45 mL, 2.45 mmol)

and THF (2.45 mL) at RT overnight. Dilute the reaction with water and extract with dichloromethane. Acidify the aqueous with 5 N HCl, extract the aqueous with dichloromethane and dry (magnesium sulfate) and concentrate to give the title compound (106 mg, 74%).

MS (ES): $m/z = 293$ [M+H].

Preparation 88

3,5-Bis(methyl-propylcarbamoyl)-benzoic acid

3,5-Bis(methyl-propylcarbamoyl)-benzoic acid ethyl ester

Stir a solution of 5-(methyl-propylcarbamoyl)-isophthalic acid monoethyl ester (146 mg, 0.5 mmol), 1-hydroxybenzotriazole (68 mg, 0.5 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg, 0.5 mmol), N-methylpropylamine (51 µL, 0.5 mmol) in dichloromethane (2.5 mL) at RT overnight. Dilute with dichloromethane (15 mL) and wash with water (5 mL), 0.1 N citric acid (5 mL), saturated aqueous sodium bicarbonate (5 mL), and saturated aqueous sodium chloride (5 mL). Dry (magnesium sulfate) and concentrate to give the title compound (157 mg, 90%)

MS (ES): $m/z = 349$ [M+H].

3,5-Bis(methyl-propylcarbamoyl)-benzoic acid

Stir a solution of 3,5-bis(methyl-propylcarbamoyl)-benzoic acid ethyl ester (157 mg, 0.45 mmol), 1 N lithium hydroxide (2.25 mL, 2.25 mmol) and THF (2.25 mL) for 2 h at RT. Dilute the reaction with water (10 mL) and extract with dichloromethane (10 mL). Acidify the aqueous with 5 N HCl, extract the aqueous with dichloromethane, dry (magnesium sulfate) and concentrate to give the title compound (119 mg, 82%).

MS (ES): $m/z = 321$ [M+H].

Preparation 89

5-(Methyl-propylcarbamoyl)-isophthalic acid monoisopropyl ester

5-(Methyl-propylcarbamoyl)-isophthalic acid 1-ethyl ester 3-isopropyl ester

Sonicate a mixture of 5-(methyl-propyl-carbamoyl)-isophthalic acid monoethyl ester (146 mg, 0.5 mmol), isopropanol (0.75 mL) and concentrated sulfuric acid (25 µL)

then stir the resulting solution at RT for one month. Add 1-hydroxybenzotriazole (68 mg, 0.5 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg, 0.5 mmol), and triethylamine (100 μL). Stir overnight at RT. Add dichloromethane (25 mL) and wash with 0.1 N citric acid (5 mL), saturated aqueous sodium bicarbonate (10 mL), saturated aqueous sodium chloride (10 mL), dry (magnesium sulfate) and concentrate (149 mg, 89%).

MS (ES): $m/z = 336$ [M+H].

5-(Methyl-propylcarbamoyl)-isophthalic acid monoisopropyl ester

Stir a solution of 5-(methyl-propylcarbamoyl)-isophthalic acid 1-ethyl ester 3-isopropyl ester (149 mg, 0.4 mmol) in 0.2 N NaOH in 1:10 water:isopropanol (2.2 mL) overnight. Add 1 N lithium hydroxide (0.44 mL) and stir for 1 h at RT. Dilute with water and extract with dichloromethane. Acidify the aqueous with 5 N HCl, extract the aqueous with dichloromethane, dry (magnesium sulfate) and concentrate to give the title compound (79 mg, 56%).

MS (ES): $m/z = 308$ [M+H].

Preparation 90

5-Difluoromethyl-N-methyl-N-propyl-isophthalamic acid

5-Hydroxymethyl-isophthalic acid monoethyl ester

Add a solution of diethyl-5-(hydroxymethyl)-isophthalate (5 g, 19.8 mmol) in acetone (88 mL) to a solution of NaOH (792 mg, 19.8 mmol) in ethanol (12 mL). After 4 h collect precipitate. Dissolve the precipitate in water (200 mL), add 5 N HCl to about about pH = 1 and collect the precipitate. Extract the aqueous with dichloromethane, combine the extracts with the precipitate and concentrate to give to give the title compound (1.9 g, 43%)

MS (ES): *m/z* = 225 [M+H].

5-Hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Stir a solution of 5-hydroxymethyl-isophthalic acid monoethyl ester (1.9 g, 8.4 mmol), N-methylpropylamine (947 µl, 9.2 mmol), 1-hydroxybenzotriazole (1.24 g, 9.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.77 g, 9.2 mmol) in a mixture of dichloromethane (12 mL) and DMF (12 mL) at RT for 1.5 h. Concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound (950 mg, 40% yield).

MS (ES): *m/z* = 280 [M+H].

5-Formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Add a solution of 5-hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (600 mg, 2.15 mmol) dropwise to a mixture of Dess-Martin periodinane (1.06 g, 2.5 mmol) in dichloromethane (6.5 mL). Stir the exothermic reaction mixture (32 °C) for 20 min without additional heat. To the reaction mixture add diethyl ether (12 mL) and saturated aqueous sodium bicarbonate (12 mL). Separate the layers and wash the aqueous layer with diethyl ether (2 x 12 mL). Combine the organics and wash with saturated aqueous sodium bicarbonate (12 mL), saturated aqueous sodium chloride (12 mL), dry (magnesium sulfate), concentrate, and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound as an oil (0.54 g, 91%).

MS (ES): *m/z* = 278 [M+H].

5-Difluoromethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Add a solution of bis(2-methoxyethyl) aminosulfur trifluoride (161 mg, 0.73 mmol) in dichloromethane (88 µL) to a solution of 5-formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (120 mg, 0.43 mmol) in dichloromethane (130 µL). Place the reaction under nitrogen, add ethanol (3.5 µL) and stir the reaction at RT for 48 h. Pour the reaction into saturated aqueous sodium bicarbonate and extract with dichloromethane. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound (68 mg, 53%).

MS (ES): *m/z* = 300 [M+H].

5-Difluoromethyl-N-methyl-N-propyl-isophthalamic acid

Stir a solution of 5-difluoromethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (68 mg, 0.23 mmol), 1 N lithium hydroxide (1.15 mL) and THF (1.15 mL) at RT over the weekend. Add water and extract with dichloromethane. Acidify the aqueous with 5 N HCl (240 µL), extract with dichloromethane, dry (magnesium sulfate) and concentrate to give the title compound (61 mg, 100%).

Preparation 91

5-Fluoromethyl-N-methyl-N-propyl-isophthalamic acid

5-Fluoromethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Add bis(2-methoxyethyl) aminosulfur trifluoride (220 mg, 1.0 mmol) to a polypropylene tube (5 mL), seal, cool to –78 °C, add a solution of 5-hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (250 mg, 0.9 mmol) in dichloromethane (1 mL) in 0.2 mL increments. Stir at –78 °C for 3 h then at RT overnight. Pour the reaction into saturated aqueous sodium bicarbonate. Extract with dichloromethane, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound (73 mg, 29%).

MS (ES): *m/z* = 282 [M+H].

5-Fluoromethyl-N-methyl-N-propyl-isophthalamic acid

Stir a solution of 5-fluoromethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (73 mg, 0.26 mmol), 1 N lithium hydroxide (1.3 mL, 1.3 mmol) and THF (1.3 mL) at RT overnight. Add water (10 mL) and extract with dichloromethane (3 x 10 mL). Acidify the aqueous with 5 N HCl (260 µL), extract with dichloromethane (3 x 10 mL), dry (magnesium sulfate) and concentrate to give the title compound (56 mg, 85%).

Preparation 92

N-Methyl-N-propyl-5-vinyl-isophthalamic acid

5-Bromo-isophthalic acid monomethyl ester

Add a solution of NaOH pellets (3.66g, 91.5 mmol) in methanol (200 mL) to dimethyl-5-bromoisophthalate (25 g) and stir the resulting solution overnight at RT. Add water (300 mL) and extract with dichloromethane (3 x 200 mL). Acidify the aqueous with 5 N HCl (20 mL), filter the precipitate and dry to give a mixture of the title compound and 5-bromo-isophthalic acid in about a 6:4 ratio by LCMS (18.2 g crude).

5-Bromo-N-methyl-N-propyl-isophthalamic acid methyl ester

Add N-methylpropylamine (5.14 g, 70.4 mmol) to a mixture of 5-bromo-isophthalic acid monomethyl ester and 5-bromo-isophthalic acid (18.2 g), 1-hydroxybenzotriazole (9.5 g, 70.4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (13.5 g, 70.4 mmol) in dichloromethane (200 mL). Stir the solution for 2 h at RT. Add saturated aqueous ammonium chloride (100 mL) and acidify the mixture with 1 N HCl. Filter away the precipitate, extract the filtrate with dichloromethane, wash the organic extracts with 1 N HCl, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 30:70 ethyl acetate:hexanes) to give the title compound as an oil (10.1 g, 46%).

MS (ES): m/z = 315 [M+H].

N-Methyl-N-propyl-5-vinyl-isophthalamic acid methyl ester

Dissolve 5-bromo-N-methyl-N-propyl-isophthalamic acid methyl ester (2.7 g, 8.6 mmol) in toluene (16 mL) and place the solution under nitrogen. Add in sequence 2,6-di-tert-butyl-4-methylphenol (a few crystals), tetrakis(triphenylphosphine)palladium (0)

(185 mg, 0.16 mmol), and tributylvinyl tin (3 g, 9.5 mmol) and reflux for 4 h. Filter though a filtering agent and concentrate. Add diethyl ether (70 mL) and 20% aqueous potassium fluoride (70 mL) and stir vigorously. Collect the diethyl ether layer and extract with diethyl ether two additional times. Concentrate and purify (silica gel chromatography, eluting with 0:100 to 50:50 ethyl acetate:hexanes) to give the title compound (1.58 g, 70%).

N-Methyl-N-propyl-5-vinyl-isophthalamic acid

Stir a solution of N-methyl-N-propyl-5-vinyl-isophthalamic acid methyl ester (78 mg, 0.3 mmol), 1 N lithium hydroxide (1.5 mL, 1.5 mmol), and THF (1.5 mL) at RT overnight. Add water and extract with ethyl acetate. Acidify the aqueous with 5 N HCl, extract with ethyl acetate, dry (magnesium sulfate) and concentrate to give the title compound (52 mg, 70%).

Preparation 93

N-Methyl-5-oxazol-2-yl-N-propyl-isophthalamic acid

N-Methyl-5-oxazol-2-yl-N-propyl-isophthalamic acid methyl ester

Add n-butyllithium (1.6 M in hexanes, 1.25 mL, 2.01 mmol) dropwise to a solution of oxazole (126 mg, 1.83 mmol) in THF (12.6 mL) at –78 °C. Stir for 30 min at –78 °C and add a solution of zinc chloride (747 mg, 5.49 mmol) in diethyl ether (5.5 mL) and stir at 0 °C for 1 h. Add a solution of 5-iodo-N-methyl-N-propyl-isophthalamic acid methyl ester (330 mg, 0.91 mmol) in THF (5.1 mL) followed by tetrakis(triphenylphosphine)palladium (0) (105 mg, 0.091 mmol) and heat to reflux for 30 min. Add ethyl acetate (40 mL), wash with water (2 x 20 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexane) to give the title compound (225 mg, 82%).
MS (ES): m/z = 303 [M+H].

N-Methyl-5-oxazol-2-yl-N-propyl-isophthalamic acid

Stir a solution of N-methyl-5-oxazol-2-yl-N-propyl-isophthalamic acid methyl ester (225 mg, 0.74 mmol) in 1 N lithium hydroxide (3.0 mL, 3.0 mmol) and THF (3.0 mL) at RT for 3 h. Add water (40 mL) and extract with ethyl acetate (40 mL). Acidify

the aqueous with 5 N HCl, extract with ethyl acetate (2 x 40 mL), dry (magnesium sulfate) and concentrate to give the title compound (213 mg, 100%).

Preparation 94

N-Methyl-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-N-propyl-isophthalamic acid

N-Methyl-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-N-propyl-isophthalamic acid ethyl ester

Stir a solution of 5-(methyl-propyl-carbamoyl)-isophthalic acid monoethyl ester (330 mg, 1.13 mmol), acetamideoxime (117 mg, 1.58 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (303 mg, 1.58 mmol) in dichloromethane (20 mL) at RT overnight. Concentrate and purify (silica gel chromatography, eluting with 2:98 methanol:dichloromethane). Concentrate and add THF (30 mL) and 1 N tetrabutylammonium fluoride in THF (43 µL, 0.043 mmol). Reflux the solution for 30 min and concentrate. Add ethyl acetate, extract with saturated aqueous sodium chloride, dry (magnesium sulfate) concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound (135 mg, 36%).

MS (ES): m/z = 332 [M+H].

N-Methyl-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-N-propyl-isophthalamic acid

Stir a solution of N-methyl-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-N-propyl-isophthalamic acid ethyl ester (135 mg, 0.4 mmol), 1 N lithium hydroxide (1.6 mL, 1.6 mmol) and THF (1.6 mL) at RT overnight. Add 1 N HCl (20 mL) and extract with ethyl acetate (3 x 20 mL). Dry (magnesium sulfate) and concentrate to give the title compound.

Preparation 95

N-Methyl-5-oxazol-5-yl-N-propyl-isophthalamic acid

N-Methyl-5-oxazol-5-yl-N-propyl-isophthalamic acid

Heat a solution of 5-formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (300 mg, 1.08 mmol), tosylmethyl isocyanide (254 mg, 1.3 mmol), and sodium methoxide (193 mg, 3.57 mmol) in methanol (3.1 mL) at 40 °C for 1 h. Add water to the hot solution and extract with dichloromethane and ethyl acetate. Acidify the aqueous with 5 N HCl, extract with dichloromethane, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 4:96 methanol:dichloromethane) to give the title compound (203 mg, 65%).

MS (ES): m/z = 289 [M+H].

Preparation 96

5-(2,2-Difluorovinyl)-N-methyl-N-propyl-isophthalamic acid

Toluene-4-sulfonic acid 2,2-difluorovinyl ester

Add n-butyllithium (1.6 M in hexanes, 4.9 mL, 7.8 mmol) dropwise over 5 min to a solution of 2,2,2-trifluoroethyl-p-toluene sulfonate (1.0 g, 3.9 mmol) in THF (20 mL) at –78 °C. Stir for 30 min, add acetic acid (225 µL, 3.9 mmol) and stir for 30 min. Warm to RT, add ethyl acetate and extract with saturated aqueous ammonium chloride, and saturated aqueous sodium bicarbonate. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 15:85 ethyl acetate:hexanes) to give the title compound as an oil (430 mg, 47%).

5-(2,2-Difluorovinyl)-N-methyl-N-propyl-isophthalamic acid ethyl ester

Add n-butyllithium (1.6 M in hexanes, 4.5 mL, 7.4 mmol) dropwise to a mixture of zirconocene dichloride (1.05 g, 3.6 mmol) in dry THF (15 mL) at –78 °C and stir for 1 h. Add a solution of toluene-4-sulfonic acid 2,2-difluorovinyl ester (420 mg, 1.8 mmol) in THF (3.6 mL) dropwise. Stir at –78 °C for 5 min and at RT for 3 h. Add triphenyl phosphine (79 mg, 0.3 mmol) and tris(dibenzylidineacetone)dipalladium(0) (34 mg, 0.036 mmol), stir for 10 min, add 5-iodo-N-methyl-N-propyl-isophthalamic acid methyl ester (722 mg, 2.0 mmol) and zinc iodide (1.35 g, 4.3 mmol). Reflux the reaction for1 h and stir at RT overnight. Add pH = 7 phosphate buffer (400 mL) and ethyl acetate (250 mL).

Separate the layers and wash with saturated aqueous ammonium chloride (2 x 100 mL), saturated aqueous sodium bicarbonate (2 x 100 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 25:75 ethyl acetate:hexanes) to give the title compound (187 mg, 35%).
MS (ES): $m/z = 298$ [M+H].

5-(2,2-Difluorovinyl)-N-methyl-N-propyl-isophthalamic acid

Stir a solution of 5-(2,2-difluorovinyl)-N-methyl-N-propyl-isophthalamic acid ethyl ester (187 mg, 0.63 mmol), 1 N lithium hydroxide (2.5 mL, 2.5 mmol) and THF (2.5 mL) at RT overnight. Partition the reaction between ethyl acetate and water. Acidify the aqueous with 5 N HCl and extract with ethyl acetate. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 2:98 to 6:94 methanol:dichloromethane with 1% acetic acid) to give the title compound (78 mg, 44%).
MS (ES): $m/z = 284$ [M+H].

Preparation 97

N-Methyl-5-(2-methylpyrrolidine-1-carbonyl)-N-propyl-isophthalamic acid

N-Methyl-5-(2-methylpyrrolidine-1-carbonyl)-N-propyl-isophthalamic acid ethyl ester

Add 2-methyl pyrrolidine (204 mg, 2.4 mmol) to a solution of 5-(methyl-propylcarbamoyl)-isophthalic acid monoethyl ester (640 mg, 2.18 mmol) in dichloromethane (8 mL) followed by 1-hydroxybenzotriazole (20 mg, 0.15 mmol) and diisopropyl carbodiimide (375 µL, 2.4 mmol). Stir the solution at RT over the weekend. Add ethyl acetate (25 mL) and wash with saturated aqueous ammonium chloride (2 x 10 mL), saturated aqueous sodium bicarbonate (10 mL), saturated aqueous sodium chloride (10 mL), dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound as an oil (218 mg, 28%).
MS (ES): $m/z = 361$ [M+H].

N-Methyl-5-(2-methylpyrrolidine-1-carbonyl)-N-propyl-isophthalamic acid

Stir a solution of N-methyl-5-(2-methylpyrrolidine-1-carbonyl)-N-propyl-isophthalamic acid ethyl ester (218 mg, 0.6 mmol), 1 N lithium hydroxide (2.4 mL, 2.4 mmol) and THF (2.4 mL) at RT overnight. Add 50 mL water and extract with

dichloromethane (3 x 10 mL). Acidify the aqueous with 1 N HCl (3 mL) and extract with dichloromethane (3 x 10 mL). Dry (sodium sulfate) and concentrate to give the title compound (216 mg, 100%).
MS (ES): m/z = 333 [M+H].

Preparation 98

5-(3,3-Difluoropyrrolidine-1-carbonyl)-N-methyl-N-propyl-isophthalamic acid

3,3-Difluoropyrrolidine-1-carboxylic acid tert-butyl ester

Add ethanol (270 µL) to a solution of 3-oxopyrrolidine-1-carboxylic acid tert-butyl ester (3.36 g, 18.2 mmol), and bis(2-methoxyethyl) aminosulfur trifluoride (6.85 g, 31 mmol) in dichloromethane in a polypropylene tube. Stir the exothermic reaction at RT overnight. Add dichloromethane (100 mL) and wash with saturated aqueous sodium bicarbonate (2 x 20 mL), saturated aqueous sodium chloride (20 mL), dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 5:95 acetone:hexanes to give the title compound as an oil (2.18 g, 58%).
MS (ES): m/z = 347 [M+H].

3,3-Difluoropyrrolidine hydrochloride

Stir a solution of 3,3-difluoropyrrolidine-1-carboxylic acid tert-butyl ester (2.18 g, 10.5 mmol) in hydrogen chloride (4 N in 1,4-dioxane, 65 mL) at RT. Concentrate to give the title compound (1.5 g, 97%).

5-(3,3-Difluoropyrrolidine-1-carbonyl)-N-methyl-N-propyl-isophthalamic acid ethyl ester

Dissolve 5-(methyl-propylcarbamoyl)-isophthalic acid monoethyl ester (667 mg, 2.3 mmol) in a 0.1 N 1-hydroxybenzotriazole solution of 1:1:5 tert-butanol:acetonitrile:dichloromethane (23 mL, 2.3 mmol). Stir the solution at RT for 5 min, add 3,3-difluoropyrrolidine hydrochloride (331 mg, 2.3 mmol) and triethylamine (640 µL, 4.6 mmol). Stir the reaction at RT for 2 h, add ethyl acetate (100 mL) and wash with saturated aqueous ammonium chloride (2 x 30 mL), saturated aqueous sodium chloride (30 mL), dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound (270 mg, 31%).

MS (ES): *m/z* = 283 [M+H].

5-(3,3-Difluoropyrrolidine-1-carbonyl)-N-methyl-N-propyl-isophthalamic acid

Stir a solution of 5-(3,3-difluoropyrrolidine-1-carbonyl)-N-methyl-N-propyl-isophthalamic acid ethyl ester (270 mg, 0.71 mmol), 1 N lithium hydroxide (1.1 mL, 1.1 mmol) and THF (2.0 mL) at RT for 4 h. Add 10 mL water, acidify with 1 N HCl (2 mL), extract with dichloromethane (3 x 10 mL), dry (sodium sulfate) and concentrate to give the title compound (262 mg, 100%).

Preparation 99

5-Chloro-N-methyl-N-propyl-isophthalamic acid

5-Chloro-N-methyl-N-propyl-isophthalamic acid

Dissolve commercially available 5-chloroisophthalic acid dimethyl ester (1.0 g, 4.37 mmol) in acetone (10 mL) and add a solution of NaOH (192 mg, 4.81 mmol) in methanol (2 mL). Stir 3 h and concentrate. Partition the residue between diethyl ether and water. Acidify the water layer to about pH = 1 and collect the precipitate, 5-chloro-isophthalic acid monomethyl ester (675 mg, 72%). Dissolve 5-chloro-isophthalic acid monomethyl ester (459 mg, 2.13 mmol) in DMF (20 mL), add 1-(3-dimethylamino-propyl)-3-ethyl-carbodiimide hydrochloride (513 mg, 2.67 mmol) and 1-hydroxybenzotriazole (360 mg, 2.67 mmol). Stir at RT 1 h and add methyl propylamine (584 mg, 8.0 mmol). Stir at RT 3 h, dilute with ethyl acetate, wash with 10% aqueous potassium carbonate, 0.1 N citric acid, 1 N lithium chloride and saturated aqueous sodium chloride and concentrate. Dissolve the residue in THF (30 mL) and add 1 N lithium hydroxide (10 mL, 10 mmol). Stir at RT 3 h and acidify to about pH = 1 by addition of 1 N HCl. Extract with diethyl ether, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): *m/z* = 256.1 [M+H].

Preparation 100

N,N-Dipropyl-isophthalamic acid

Dissolve isophthalic acid monomethyl ester (2.25 g, 12.5 mmol), 1-(3-dimethylamino-propyl)-3-ethyl-carbodiimide hydrochloride (2.88 g, 15 mmol), 1-

hydroxybenzotriazole (2.02 g, 15 mmol) and triethylamine (3.03g, 30 mmol) in THF (50 mL) and DMF (20 mL). Stir at RT 15 min and add dipropylamine (1.52 g, 15 mmol). Stir at RT 16 h and dilute with ethyl acetate. Wash with 10% aqueous potassium carbonate, 0.1 N citric acid, 1 N lithium chloride and saturated aqueous sodium chloride and concentrate. Dissolve the residue in THF (60 mL), methanol (18 mL) and water (9 mL). Add lithium hydroxide (2.1 g, 50 mmol), stir at RT 16 h and concentrate. Partition the residue between diethyl ether and 1 N HCl. Dry (magnesium sulfate) and concentrate to give the title compound as a solid.

MS (ES): *m/z* 250.2 [M+H].

Preparation 101

N-Methyl-5-propoxy-N-propyl-isophthalamic acid

5-Propoxy-isophthalic acid monomethyl ester

Heat commercially available 5-hydroxy-isophthalic acid dimethyl ester (1.0 g, 4.8 mmol), potassium carbonate (5.25 g, 38 mmol) and iodopropane (1.36 g, 8.0 mmol) in DMF (20 mL) at 70 °C for 8 h. Cool to RT, partition between ethyl acetate and 10% aqueous potassium carbonate. Wash the ethyl acetate layer with 1 N lithium chloride, saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate. Dissolve the residue in acetone (10 mL) and add a solution of NaOH (192 mg, 4.80 mmol) in methanol (2 mL). Stir at RT 16 h and concentrate. Partition between diethyl ether and 0.1 N citric acid, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): *m/z* = 239.0 [M+H].

N-Methyl-5-propoxy-N-propyl-isophthalamic acid

Mix 5-propoxy-isophthalic acid monomethyl ester (500 mg, 2.10 mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (403 mg, 2.10 mmol) and 1-hydroxybenzotriazole (283 mg, 2.10 mmol) in DMF (15 mL) at RT 1 h. Add methylpropylamine (438 mg, 6.0 mmol) and stir at RT 16 h. Dilute with ethyl acetate, wash with 10% aqueous potassium carbonate, 0.1 N citric acid, 1 N lithium chloride and saturated aqueous sodium chloride. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 20:80 to 30:70 ethyl acetate:hexanes) to give the carboxamide. Dissolve the residue (265 mg, 0.90 mmol) in THF (10 mL) and add 1 N lithium hydroxide (5 mL, 5 mmol) and stir at RT 16 h. Acidify the solution to about pH = 1 with 1 N HCl, extract with ethyl acetate, dry (magnesium sulfate) and concentrate to give the title compound as a solid.

MS (ES): m/z = 280.0 [M+H].

Preparation 102

5-Methanesulfonyl-N-methyl-N-propyl-isophthalamic acid

5-Methanesulfonyl-isophthalic acid dimethyl ester

Dissolve sodium sulfite (1.7 g, 13.51 mmol) and sodium bicarbonate (1.2 g, 14.19 mmol) in water (10 mL). Add 5-chlorosulfonyl-isophthalic acid dimethyl ester (2.0 g, 6.76 mmol) and ethanol (2 mL). Heat to 50 °C for 2 h, concentrate and dry the solid. Add DMF (40 mL) and iodomethane (4.56 g, 32 mmol) and stir at RT for 3 h. Dilute with ethyl acetate, wash with 10% aqueous potassium carbonate, 1 N lithium chloride and saturated aqueous sodium chloride. Dry (magnesium sulfate) and concentrate to give the title compound as a solid.

^{1}H NMR (CDCl3) δ 8.93 (s, 1H), 8.76 (s, 2H), 4.00 (s, 6H), 3.13 (s, 3H).

5-Methanesulfonyl-N-methyl-N-propyl-isophthalamic acid

Dissolve 5-methanesulfonyl-isophthalic acid dimethyl ester (1.45 g, 5.33 mmol) in acetone (16 mL) and add a solution of NaOH (210 mg, 5.33 mmol) in methanol (2.5 mL). Stir at RT 1 h and concentrate. Partition between diethyl ether and water. Acidify the water layer to about pH = 1 with 1 N HCl. Collect and dry the white precipitate. Dissolve the precipitate (500 mg, 1.95 mmol) in DMF (20 mL), add 1-(3-dimethylamino-

propyl)-3-ethyl-carbodiimide hydrochloride (374 mg, 1.95 mmol) and 1-hydroxybenzotriazole (263 mg, 1.95 mmol) and stir at RT 40 min. Add methyl-propylamine (568 mg, 7.78 mmol) and stir at RT 14 h. Dilute with ethyl acetate, wash with 10% aqueous potassium carbonate, 0.1 N citric acid, 1 N lithium chloride and saturated aqueous sodium chloride. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 to 0:100 ethyl acetate:hexanes) to give the amide ester intermediate (340 mg). Dissolve in THF (10 mL) and add 1 N lithium hydroxide (5 mL, 5 mmol). Stir at RT 3 h and pour into 1 N HCl (20 mL). Extract with ethyl acetate, wash with saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate to give the title compound as a solid.

MS (ES): $m/z = 300.1$ [M+H].

Preparation 103

5-Dimethylsulfamoyl-isophthalic acid monomethyl ester

Dissolve commercially available 5-chlorosulfonyl-isophthalic acid dimethyl ester (422 mg, 1.43 mmol) in THF (10 mL) and add dimethylamine (2.0 M in THF, 2.5 mL, 5 mmol). Stir at RT 3 h, dilute with ethyl acetate, wash with 10% aqueous potassium carbonate, 0.1 N citric acid and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate. Dissolve the residue in acetone (10 mL) and methanol (5 mL). Add a solution of NaOH (60 mg, 1.43 mmol) in methanol (0.7 mL). Stir at RT 16 h and acidify with 1 N HCl to about pH = 1. Partition between ethyl acetate and water, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): m/z 288.0 [M+H].

Preparation 104

N-methyl-5-(2-methylpropenyl)-N-propyl-isophthalamic acid

5-(2-Methylpropenyl)-isophthalic acid diethyl ester

Dissolve commercially available 5-hydroxymethyl-isophthalic acid diethyl ester (2.0 g, 7.91 mmol) in dichloromethane (30 mL) and add this solution to Dess-Martin periodinane (3.69 g, 8.71 mmol) in dichloromethane (30 mL). Stir 30 min at RT and pour into saturated aqueous sodium bicarbonate (100 mL) containing sodium thiosulfate (25 g). Extract with diethyl ether (200 mL), dry (magnesium sulfate), concentrate and purify

(silica gel plug, washing with 20:80 ethyl acetate:hexanes) to give the aldehyde. Suspend isopropyltriphenylphosphonium iodide (4.76g, 11 mmol) in THF (40 mL). Add potassium tert-butoxide (1.23 g, 11 mmol), then a solution of the aldehyde prepared above in THF (40 mL). Stir at RT for 30 min, dilute with water and ethyl acetate. Wash the organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 5:95 ethyl acetate:hexanes) to give the title compound as an oil (535 mg, 25%).

^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 8.07 (s, 2H), 6.31 (s, 1H), 4.40 (q, J = 6.8 Hz, 4H), 1.93 (s, 3H), 1.87 (s, 3H), 1.41 (t, J = 6.8 Hz, 6H).

N-Methyl-5-(2-methylpropenyl)-N-propyl-isophthalamic acid

Dissolve 5-(2-methylpropenyl)-isophthalic acid diethyl ester (535 mg, 1.94 mmol) in acetone (10 mL) and add a solution of NaOH (77 mg, 1.94 mmol) in methanol (2 mL). Stir at RT 2 days and concentrate. Dissolve in water and wash with diethyl ether. Acidify the water layer to about pH = 1 with 1 N HCl and extract with dichloromethane. Dry the dichloromethane layer over magnesium sulfate, filter and concentrate. Dissolve the residue in DMF (10 mL) and add 1-(3-dimethylamino-propyl)-3-ethyl-carbodiimide hydrochloride (409 mg, 2.13 mmol) and 1-hydroxybenzotriazole (288 mg, 2.13 mmol). After 30 min, add methyl-propyl-amine (283 mg, 3.87 mmol) and triethylamine (665 mg, 6.58 mmol) in DMF (2 mL). Stir at RT 1 h and dilute with ethyl acetate. Wash with 10% aqueous potassium carbonate, 0.1 N citric acid, 1 N lithium chloride and saturated aqueous sodium chloride and concentrate. Dissolve the residue in THF (20 mL) and add 1 N lithium hydroxide (10 mL, 10 mmol). Stir at RT for 4 h and acidify to about pH = 1 with 1 N HCl. Extract with dichloromethane, dry (magnesium sulfate), filter and concentrate to give the title compound as a solid (220 mg, 41%).

MS (ES): *m/z* 276.1 = [M+H].

Preparation 105

6-Fluoro-5-methanesulfonyl-N-methyl-N-propyl-isophthalamic acid

3-Bromo-5-chlorosulfonyl-4-fluorobenzoic acid

Heat 3-bromo-4-fluorobenzoic acid (6.25 g, 26.2 mmol) in chlorosulfonic acid (15 mL) at 125 °C for 120 h. Cool to RT and add dropwise to about 125 mL ice water. Collect the filtered solid as the title compound.

MS (ES): m/z = 317.1 [M+H].

3-Bromo-4-fluoro-5-methanesulfonylbenzoic acid

To sodium thiosulfite (2.6 g, 20.7 mmol) and sodium bicarbonate (1.74 g, 20.7 mmol) in water (20 mL) at 75 °C add 3-bromo-5-chlorosulfonyl-4-fluorobenzoic acid (6.25 g, 19.7 mmol) in portions over 5 min. After 1 h, cool to RT and add chloroacetic acid (5.29 g, 56 mmol) and NaOH (1.18 g, 29.5 mmol) and reflux 16 h. Cool to RT and collect the title compound as a solid

MS (ES): m/z = 297.1 [M+H].

3-Bromo-4-fluoro-5-methanesulfonyl-N-methyl-N-propyl-benzamide

Mix 3-bromo-4-fluoro-5-methanesulfonylbenzoic acid (1.6 g, 5.04 mmol), 1-(3-dimethylamino-propyl)-3-ethyl-carbodiimide hydrochloride (968 mg, 5.04 mmol) and 1-hydroxybenzotriazole (680 mg, 5.04 mmol) in DMF (20 mL) at RT for 20 min. Add methyl-propylamine (368 mg, 5.04 mmol) and triethylamine (520 mg, 15.1 mmol) and stir at RT for 1 h. Dilute with ethyl acetate, wash with 10% aqueous potassium carbonate, 0.1 N citric acid, 1 N lithium chloride and saturated aqueous sodium chloride, concentrate and purify (silica gel chromatography, eluting with 10:90 to 50:50 ethyl acetate:hexanes) to give the title compound as an oil.

MS (ES): m/z = 352.0, 354.0 [M+H].

6-Fluoro-5-methanesulfonyl-N-methyl-N-propyl-isophthalamic acid

Mix 3-bromo-4-fluoro-5-methanesulfonyl-N-methyl-N-propyl-benzamide (1.36 g, 3.86 mmol), palladium acetate (337 mg, 1.5 mmol) and 1,4-bis(diphenylphosphino)-butane (1.35 g, 3.17 mmol) in DMSO (60 mL), tert-butanol (40 mL), triethylamine (3.88mL) and water (0.22 mL) under an atmosphere of carbon monoxide (100 psi) at 90

°C for 18 h. Cool to RT and filter. Pour the mixture into water and wash thoroughly with ethyl acetate. Extract the organic layer with 10% aqueous potassium carbonate. Acidify the aqueous layer and extract with ethyl acetate. Dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): $m/z = 318.0$ [M+H].

Preparation 106

5-(Methanesulfonyl-methylamino)-N-methyl-N-propyl-isophthalamic acid

5-Amino-N-methyl-N-propyl-isophthalamic acid methyl ester

Mix 5-nitro-isophthalic acid monomethylester (3.0 g, 13.32 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.20 g, 16.65 mmol), and 1-hydroxybenzotriazole (2.25 g, 16.65 mmol) in dichloromethane (100 mL) at RT for 20 min. Add propylmethylamine (1.46 g, 16.65 mmol) and triethylamine (3.36 g, 33.3 mmol). Stir at RT for 1 h, dilute with ethyl acetate, wash with 10% aqueous potassium carbonate, 1 N citric acid, saturated aqueous sodium chloride and concentrate. Dissolve in ethanol (100 mL), add a slurry of 10% Pd/C (300 mg) in ethanol (10mL) and place under a hydrogen atmosphere using a balloon and stir overnight. Flush with nitrogen, filter and concentrate to give the title compound as an oil.

MS (ES): $m/z = 251.1$ [M+H].

5-Methanesulfonylamino-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve 5-amino-N-methyl-N-propyl-isophthalamic acid methyl ester (1.64 g, 6.55 mmol) in dichloromethane (20 mL) and add pyridine (620mg, 6.88 mmol) and methanesulfonyl chloride (788 mg, 6.88 mmol). Stir at RT for 72 h, dilute with dichloromethane, wash with 0.1 N citric acid and saturated aqueous sodium chloride. Dry (magnesium sulfate) and concentrate to give the title compound as an oil.

MS (ES): $m/z = 329.1$ [M+H].

5-(Methanesulfonyl-methylamino)-N-methyl-N-propyl-isophthalamic acid methyl ester

Mix 5-methanesulfonylamino-N-methyl-N-propyl-isophthalamic acid methyl ester (2.09 g, 6.36 mmol), iodomethane (1.35 g, 9.55 mmol), potassium carbonate (1.38 g, 10 mmol), and tetrabutylammonium bromide (206 mg, 0.64 mmol) in DMF (10 mL) at RT for 30 min. Dilute with ethyl acetate and wash with 10% aqueous potassium carbonate, 1 N lithium chloride and saturated aqueous sodium chloride. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 40:60 ethyl acetate:dichloromethane) to give the title compound as an oil.

MS (ES): m/z = 343.1 [M+H].

5-(Methanesulfonyl-methylamino)-N-methyl-N-propyl-isophthalamic acid

Dissolve 5-(methanesulfonyl-methylamino)-N-methyl-N-propyl-isophthalamic acid methyl ester (1.09 g, 3.18 mmol) in THF (80 mL) and add 1 N NaOH (16 mL, 16 mmol). Stir at RT for 16 h and add 5 N HCl (5 mL). Dilute with ethyl acetate, wash with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): m/z = 329.1 [M+H].

Preparation 107

5-Acetylamino-N-methyl-N-propyl-isophthalamic acid methyl ester

5-Acetylamino-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve 5-amino-N-methyl-N-propyl-isophthalamic acid methyl ester (1.64 g, 6.55 mmol) in dichloromethane (20mL) and add triethylamine (0.993 g, 9.83 mmol), then acetyl chloride (772 mg, 9.83 mmol). Stir at RT for 1 h, add N,N-dimethylamino propylamine (0.5 mL), stir 10 min, dilute with dichloromethane, wash with 1 N HCl and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate to give the title compound as a solid.

MS (ES): m/z = 293.1 [M+H].

5-Acetylamino-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve 5-acetylamino-N-methyl-N-propyl-isophthalamic acid methyl ester (1.35 g, 4.62 mmol) in THF (20 mL) and add sodium hydride (0.222 g, 5.54 mmol, 60% dispersion in mineral oil) Add iodomethane (977 mg, 6.93 mmol) and stir at RT overnight. Partition between ethyl acetate and 10% aqueous potassium carbonate, wash with saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 5:95 methanol:dichloromethane) to give the N-methyl amide. Dissolve the residue in THF (60 mL) and add 1 N lithium hydroxide (20 mL). Stir at RT over the weekend. Acidify to about pH = 1 with 1 N HCl and extract with diethyl ether. Dry (magnesium sulfate) and concentrate. Dissolve the residue in dichloromethane (20 mL) and add acetyl chloride (1 mL). Stir 1 h and wash with 0.1 N HCl and saturated aqueous sodium chloride. Dry (magnesium sulfate), and concentrate to give the title compound as a solid.

MS (ES): m/z = 293.1 [M+H].

Preparation 108

5-Hydroxymethyl-N-methyl-N-propyl-isophthalamic acid

5-Hydroxymethyl-isophthalic acid monoethyl ester

Add commercially available 5-hydroxymethyl-isophthalic acid diethyl ester (5 g, 19.8 mmol) and NaOH (0.79 g, 19.8 mmol) to ethanol (100 mL). Stir for 4 h at RT. Concentrate and pour the residue into water (100 mL) and diethyl ether (100 mL). Separate the aqueous layer and wash it with diethyl ether (40 mL). Acidify the aqueous layer with 5 N HCl to about pH = 1. Extract the acidic solution with ethyl acetate (3 x 40 mL). Wash the combined organic layers with water, saturated aqueous sodium chloride, dry (sodium sulfate) and concentrate to give the title compound as a solid (3.3 g, 74%).

MS (ES): m/z = 225 [M+H].

5-Hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Mix 5-hydroxymethyl-isophthalic acid monoethyl ester (3.3 g, 14.7 mmol), N-methyl propylamine (1.5 mL, 14.7 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.8 g, 14.7 mmol), and 1-hydroxtbenzotriazole hydrate (2.0 g, 14.7 mmol) in dichloromethane (40 mL) and DMF (4 mL). Stir at RT for 3 h.

Concentrate and redissolve in ethyl acetate (150 mL). Wash with aqueous sodium bicarbonate solution, aqueous ammonium chloride solution, water, saturated aqueous sodium chloride, dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with ethyl acetate and hexanes) to give the title compound (2.5 g, 61%).
MS (ES): $m/z = 280$ [M+H].

5-Hydroxymethyl-N-methyl-N-propyl-isophthalamic acid

Mix 5-hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (1.0 g, 3.6 mmol), 1 N NaOH (25 mL) in THF (5 mL). Stir at RT overnight. Wash with diethyl ether (2 x 20 mL). Acidify the aqueous layer with 5 N HCl to about pH = 2. Extract with ethyl acetate (2 x 20 mL), concentrate and purify (silica gel chromatography eluting with 1% acetic acid in ethyl acetate and hexanes) to give the title compound (0.80 g, 89%).
MS (ES): $m/z = 252$ [M+H].

Preparation 109

5-Isopropoxymethyl-N-methyl-N-propyl-isophthalamic acid

5-Isopropoxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Mix dichloromethane (1.8 mL), pyridine (56 µL, 0.7 mmol), and trifluomethanesulfonic anhydride (97 µL, 0.58 mmol) to a flask at –35 to –45 °C. Add premixed 5-hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (65 mg, 0.23 mmol) in dichloromethane (4 mL) dropwise at –40 °C. Stir for 5 min and quench with isopropyl alcohol (2 mL). Dilute the reaction mixture with dichloromethane (10 mL), wash with water (2 x 10 mL), and concentrate to give the title compound and used directly in the next step without further purification.
MS (ES): $m/z = 322$ [M+H].

5-Isopropoxymethyl-N-methyl-N-propyl-isophthalamic acid

Dissolve the crude 5-isopropoxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (0.23 mmol) in 5 N NaOH (1 mL) and methanol (2 mL). Stir at RT for 15 min, concentrate methanol and redissolve the residue in water (20 mL). Wash with diethyl ether (2 x 10 mL), acidify the aqueous layer with 5 N HCl to about pH = 1. Extract with dichloromethane to give the title compound.

MS (ES): *m/z* = 294 [M+H].

Preparation 110

5-Isopropoxy-N-methyl-N-propyl-isophthalamic acid

5-Isopropoxy-isophthalic acid dimethyl ester

Stir 5-hydroxy-isophthalic acid dimethyl ester (4 g, 19.0 mmol), 2-iodopropane (10.2 mL, 101 mmol), and potassium carbonate (4 g, 28.9 mmol) in acetone (20 mL) at 60 °C overnight. Cool to RT and pour into ethyl acetate (100 mL) and 5% aqueous ammonium chloride solution (100 mL). Separate the organic layer and wash it with water, saturated aqueous sodium chloride, dry (sodium sulfate), and concentrate to give the title compound and which is used directly in the next step without further purification. ^{1}HNMR ($CDCl_3$) δ 8.24 (d, J = 0.8 Hz, 1H), 7.72 (s, 2H), 4.68-4.62 (m, 1H), 3.93 (s, 6H), 1.35 (d, J = 6 Hz, 6H).

5-Isopropoxy-isophthalic acid monomethyl ester

Stir 5-isopropoxy-isophthalic acid dimethyl ester (3.7 g, 14.7 mmol) and NaOH (0.56 g, 14 mmol) in methanol (100 mL) and water (2 mL) overnight at RT. Concentrate methanol and redissolve the residue in diethyl ether (100 mL) and water (100 mL). Separate the layers and wash with diethyl ether. Concentrate the diethyl ether layer and recover 5-isopropoxy-isophthalic acid dimethyl ester (0.45 g). Acidify the aqueous layer with 5 N HCl to about pH = 2, extract with ethyl acetate (3 x 50 mL). Wash the combined organic layers with saturated aqueous sodium chloride, dry (sodium sulfate) and concentrate to give the title compound (3.0 g, 86%).

MS (ES): *m/z* = 237 [M+H].

5-Isopropoxy-N-methyl-N-propyl-isophthalamic acid methyl ester

Mix 5-isopropoxy-isophthalic acid monomethyl ester (3 g, 12.7 mmol), methyl propyl amine (1.3 mL, 12.7 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.4 g, 12.7 mmol), and 1-hydroxybenzotriazole hydrate (1.7 g, 12.7 mmol) in dichloromethane (50 mL) and stir overnight at RT. Dilute with dichloromethane (50 mL), wash with water, 5% aqueous ammonium chloride solution, 5% aqueous sodium

bicarbonate solution, dry (sodium sulfate) and concentrate to give the title product which is used directly without further purification.

MS (ES): m/z = 294 [M+H].

5-Isopropoxy-N-methyl-N-propyl-isophthalamic acid

Dissolve crude 5-isopropoxy-N-methyl-N-propyl-isophthalamic acid ethyl ester (12.7 mmol) in 1 N lithium hydroxide (50 mL) and THF (50 mL). Stir at RT for 4 h. Dilute with water (100 mL). Wash with diethyl ether (3 x 30 mL), and acidify the aqueous layer with 5 N HCl to about pH = 1. Extract with ethyl acetate to give the title compound (3.1 g, 87% over 2 steps).

MS (ES): m/z = 280 [M+H].

The compounds of Preparation 111-112 may be prepared essentially as described in Preparation 110 using pyrrolidine or piperidine as the amine.

Prep	Compound	MS (ES) [M+H]
111	N-Methyl-N-propyl-5-(pyrrolidine-1-carbonyl)-isophthalamic acid	319
112	N-Methyl-5-(piperidine-1-carbonyl)-N-propyl-isophthalamic acid	333

Preparation 113

5-Methoxymethyl-N-methyl-N-propyl-isophthalamic acid

5-Methoxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Stir 5-hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (1.1 g, 3.9 mmol) in THF (20 mL). Add sodium hydride (0.78 g, 60% in mineral oil) and iodomethane (729 µL, 11.7 mmol). Stir at RT for 3 h. Concentrate to give the title product which is used directly in the next step without further purification.

MS (ES): m/z = 294 [M+H].

5-Methoxymethyl-N-methyl-N-propyl-isophthalamic acid

Dissolve the crude 5-methoxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (3.9 mmol) in 5 N NaOH (2 mL) and water (10 mL). Stir at RT for 30 min. Dilute with water (20 mL). Wash with dichloromethane, and acidify the aqueous layer with 5 N HCl to about pH = 2. Extract with dichloromethane and concentrate to give the title compound (0.96g, 93%). MS (ES): m/z = 266 [M+H].

Preparation 114

5-[1,3]Dioxolan-2-yl-N-methyl-N-propyl-isophthalamic acid

5-Formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Mix 5-hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (2.8 g, 10 mmol) and Dess-Martin periodinane (5.1 g, 12 mmol) in dichloromethane (50 mL) in an ice-bath. Stir the mixture overnight at RT. Dilute with dichloromethane (50 mL) and quench it with premixed sodium thiosulfate (1.5 g) in 5% aqueous sodium bicarbonate solution (50 mL). Filter the slurry through a filtering agent and separate the organic layer. Dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes) to give the title compound (2.2 g, 79%).
MS (ES): m/z = 278 [M+H].

5-[1,3]Dioxolan-2-yl-N-methyl-N-propyl-isophthalamic acid

Mix 5-formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (580 mg, 2.1 mmol), ethane-1,2-diol (0.35 mL, 6.3 mmol), and boron trifluoride diethyl etherate (0.2 mL, 1.6 mmol) in THF (5 mL) and stir for 1.5 h. Add additional ethane-1,2-diol (0.35 mL, 6.3 mmol) and stir for 20 min. Add 1 N NaOH (10 mL) and stir for 1 h. Add additional 5 N NaOH (1 mL) and stir for 30 min. Dilute the reaction mixture with water (10 mL) and wash with diethyl ether (2 x 10 mL). Acidify the aqueous layer with 0.5 N HCl to about pH = 5. Extract with dichloromethane (3 x 20 mL), dry (sodium sulfate) and concentrate to give the title compound as a crude residue that is used in the next step without further purification.

MS (ES): m/z = 294 [M+H].

The compounds of Preparation 115-118 may be prepared essentially as described in Preparation 114 using the appropriate diols or thiols.

Prep	Compound	MS (ES) [M+H]
115	5-[1,3]Dioxan-2-yl-N-methyl-N-propyl-isophthalamic acid	
116	5-[1,3]Dithiolan-2-yl-N-methyl-N-propyl-isophthalamic acid	
117	5-[1,3]Dithian-2-yl-N-methyl-N-propyl-isophthalamic acid	
118	N-Methyl-5-[1,3]oxathiolan-2-yl-N-propyl-isophthalamic acid	310

Preparation 119

5-Cyclopropanecarbonyl-N-methyl-N-propyl-isophthalamic acid

5-(Cyclopropyl-hydroxymethyl)-N-methyl-N-propyl-isophthalamic acid ethyl ester

Add cyclopropyl magnesium bromide (0.8 M in THF, 1.3 mL, 1.02 mmol) dropwise to a solution of 5-formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (283 mg, 1.02 mmol) in THF (5 mL) at –10 °C. After stirring at 0 °C for 1.5 h, quench the mixture with 5% aqueous ammonium chloride solution while maintaining the temperature below 5 °C. Extract with ethyl acetate (3 x 30 mL), dry (sodium sulfate) concentrate and purify (silica gel chromatography, eluting with ethyl acetate and hexanes) to give the title compound (122 mg, 38%).

MS (ES): $m/z = 320$ [M+H].

5-Cyclopropanecarbonyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Mix 5-(cyclopropyl-hydroxymethyl)-N-methyl-N-propyl-isophthalamic acid ethyl ester (122 mg, 0.38 mmol) and Dess-Martin periodinane (245 mg, 0.57) in $CDCl_3$ (5 mL) and stir at RT for 2 h. Quench the reaction mixture with premixed sodium thiosulfate (500 mg) in 5% aqueous sodium carbonate solution (5 mL). Separate the organic layer and extract the aqueous layer with dichloromethane (2 x 5 mL). Combine organic layers and concentrate to give the title compound as a crude residue which is used in the next step without further purification.

MS (ES): $m/z = 318$ [M+H].

5-Cyclopropanecarbonyl-N-methyl-N-propyl-isophthalamic acid

Stir the crude 5-cyclopropanecarbonyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (0.38 mmol) in 1 N NaOH (1 mL) and ethanol (1 mL) for 3 h at RT. Dilute the mixture with water (5 mL) and wash the aqueous solution with diethyl ether (2 x 3 mL). Acidify with 1 N HCl (1 mL) and extract with ethyl acetate (3 x 5 mL). Wash the combined organic layer with saturated aqueous sodium chloride, dry (sodium sulfate) and concentrate to give the title compound as a crude residue which is used in the next step without further purification.

MS (ES): *m/z* = 290 [M+H].

Preparation 120

N-Methyl-5-(2-oxo-pyrrolidin-1-yl)-N-propyl-isophthalamic acid

5-Iodo-isophthalic acid monomethyl ester

Dissolve 5-iodo-isophthalic acid (5 g, 15.6 mmol), NaOH (600 mg, 14.8 mmol) in a mixture of methanol (100 mL), acetone (20 mL) and water (2 mL). Stir at RT overnight. Concentrate and redissolve the residue in diethyl ether (100 mL) and water (100 mL). Separate the aqueous layer and wash with diethyl ether (50 mL). Acidify the washed solution with 5 N HCl to about pH = 1. Stir for 30 min at RT and filter off solid. Wash the solid with water and dry to give the title compound (3.7 g, 77%).

5-Iodo-N-methyl-N-propyl-isophthalamic acid methyl ester

Mix 5-iodo-isophthalic acid monomethyl ester (3.6 g,), N-methyl propyl amine (1.2 mL, 11.8 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.3 g, 11.8 mmol), and 1-hydroxtbenzotriazole hydrate (1.6 g, 11.8 mmol) in dichloromethane (40 mL) and stir at RT for 4 h. Dilute with dichloromethane (20 mL), wash with water, 5% aqueous ammonium chloride solution, 5% aqueous sodium bicarbonate solution. Dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with ethyl acetate and hexanes) to give the title compound (3.2 g, 74%).

MS (ES): *m/z* = 362 [M+H].

N-Methyl-5-(2-oxopyrrolidin-1-yl)-N-propyl-isophthalamic acid methyl ester

Mix 5-iodo-N-methyl-N-propyl-isophthalamic acid methyl ester (220 mg, 0.61 mmol), 2-pyrrolidone (56 μL, 0.73 mmol), ethane-1,2-diamine (4 μL, 0.061 mmol), cesium carbonate (398 mg, 1.22) and copper (I) iodide (12 mg, 0.061 mmol) in 1,4-dioxane (4 mL). Heat the mixture to 110°C for 1 h then stir at RT overnight. Dilute with dichloromethane and filter through a filtering agent. Concentrate and purify (silica gel chromatography, eluting with ethyl acetate and hexanes) to give the title compound (100 mg, 52%).

MS (ES): *m/z* = 319 [M+H].

N-Methyl-5-(2-oxopyrrolidin-1-yl)-N-propyl-isophthalamic acid

Stir N-methyl-5-(2-oxopyrrolidin-1-yl)-N-propyl-isophthalamic acid methyl ester (100 mg, 0.314 mmol) in 1 N NaOH (0.5 mL) and methanol (0.5 mL) at RT for 3 days. Dilute the mixture with water (1 mL) and wash the aqueous solution with diethyl ether. Acidify with 1 N HCl (0.55 mL) and extract with ethyl acetate (3 x 2 mL). Concentrate the organic layers to give the title compound as a crude residue which is used in the next step without further purification.

MS (ES): *m/z* = 305 [M+H].

Preparation 121

2'-Fluoro-5-(methyl-propylcarbamoyl)-biphenyl-3-carboxylic acid

2'-Fluoro-5-(methyl-propylcarbamoyl)-biphenyl-3-carboxylic acid methyl ester

Add 1,4-dioxane (10 mL), 5-iodo-N-methyl-N-propyl-isophthalamic acid methyl ester (0.720 g, 2.00 mmol), 2-fluorophenylboronic acid (0.364 g, 2.60 mmol), tetrakis(triphenylphosphine)palladium (0) (0.347 g, 0.300 mmol), and potassium carbonate (0.829 g, 6.00 mmol) to a sealed flask flushed with nitrogen. Heat the mixture overnight and cool to RT. Filter the mixture though a filtering agent, concentrate and purify (silica gel chromatography, eluting with 4:96 EtOAc:hexanes) to give the title compound (0.297 g, 45%).

MS (ES): *m/z* = 329.9 [M+H].

2'-Fluoro-5-(methyl-propylcarbamoyl)-biphenyl-3-carboxylic acid

Chill a solution of 2'-fluoro-5-(methyl-propylcarbamoyl)-biphenyl-3-carboxylic acid methyl ester (0.297 g, 0.903 mmol) in MeOH (2 mL) and THF (2 mL) in an ice bath. Add 2 N NaOH (1.35 mL, 2.70 mmol) to the mixture and stir at RT for 3 h. Acidify the solution to about pH = 2 and concentrate to one half of the solvent. Partition the residue between EtOAc and H_2O and extract the aqueous layer with EtOAc (2 x 15 mL). Wash the combined organic extract with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound.

MS (ES): m/z = 314.2 [M-H].

The compounds of Preparation 122-123 are prepared essentially as described in Preparation 121 using the appropriate difluorophenylboronic acid.

Prep	Compound	MS (ES) [M-H]
122	2',6'-Difluoro-5-(methyl-propylcarbamoyl)-biphenyl-3-carboxylic acid	333.2
123	2',4'-Difluoro-5-(methyl-propylcarbamoyl)-biphenyl-3-carboxylic acid	332.1

Preparation 124

N-Methyl-N-propyl-5-(pyridine-3-carbonyl)-isophthalamic acid

N-Methyl-N-propyl-5-tributylstannanyl-isophthalamic acid methyl ester

Add toluene (40 mL), 5-iodo-N-methyl-N-propyl-isophthalamic acid methyl ester (5.0 g, 13.8 mmol), bis(tributyltin) (8.3 mL, 16.6 mmol), and trans-dichlorobis(triphenylphosphine)palladium (II) (0.968 mg, 1.38 mmol) to a sealed flask flushed with nitrogen. Heat the mixture at 100 °C for 24 h and cool to RT. Filter the mixture though a filtering agent, concentrate and purify (silica gel chromatography, eluting with 10:90 to 20:80 EtOAc:hexanes) to give the title compound (4.58 g, 63%).

N-Methyl-N-propyl-5-(pyridine-3-carbonyl)-isophthalamic acid methyl ester

Add THF (3 mL), N-methyl-N-propyl-5-tributylstannanyl-isophthalamic acid methyl ester (0.524 g, 1.00 mmol), nicotinoyl chloride hydrochloride (0.232 g, 1.30 mmol), 2-(di-tert-butylphosphino)biphenyl (0.045 g, 0.151 mmol), bis(dibenzylidene-acetone)palladium (0) (029 g, 0.05 mmol) to a sealed tube flushed with nitrogen. Heat the mixture at 50 °C for 16 h and cool to RT. Filter the mixture though a filtering agent,

concentrate and purify (silica gel chromatography, eluting with 50:50 to 100:0 EtOAc:hexanes) to give the title compound (0.070 g, 21%).
MS (ES): m/z = 340.9 [M+H].

N-Methyl-N-propyl-5-(pyridine-3-carbonyl)-isophthalamic acid

Chill a solution of N-methyl-N-propyl-5-(pyridine-3-carbonyl)-isophthalamic acid methyl ester (0.070 g, 0.206 mmol) in MeOH (1 mL) and THF (1 mL) in an ice bath. Add 1 N NaOH (0.62 mL, 0.62 mmol) and stir at RT for 2 h. Acidify the solution to about pH = 2 and concentrate to one half of the solvent. Partition the residue between EtOAc and H_2O. Extract the aqueous layer with EtOAc (2 x 15 mL). Wash the combined organic extract with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (72%).
MS (ES): m/z = 326.9 [M+H].

The compound of Preparation 125 is prepared essentially as described in Preparation 124 using the appropriate nicotinoyl chloride hydrochloride.

Prep	Compound	MS (ES) [M-H]
125	N-Methyl-N-propyl-5-(pyridine-2-carbonyl)-isophthalamic acid	333.2

Preparation 126

5-(Difluorophenyl-methyl)-N-methyl-N-propyl-isophthalamic acid

N-Methyl-5-(2-phenyl-[1,3]dithian-2-yl)-N-propyl-isophthalamic acid methyl ester

Add boron trifluoride diethyl etherate (0.358 mL, 2.83 mmol) to a solution of 5-benzoyl-N-methyl-N-propyl-isophthalamic acid methyl ester (0.192 g, 0.566 mmol) in dichloromethane (3 mL) at 0 °C. Add 1, 3-propanedithiol (0.114 mL, 1.12 mmol). Stir at RT overnight. Partition between water (20 mL) and dichloromethane (20 mL) and extract the aqueous layer with dichloromethane (20 mL). Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 30:70 EtOAc:hexanes) to give the title compound (51%).
MS (ES): m/z = 430.0 [M+H].

5-(Difluorophenyl-methyl)-N-methyl-N-propyl-isophthalamic acid methyl ester

Chill a solution of nitrosonium tetrafluoroborate (0.074 g, 0.63 mmol), hydrogen fluoride-pyridine (0.250 mL) in dichloromethane (2 mL) in a plastic bottle. Add a solution of N-methyl-5-(2-phenyl-[1,3]dithian-2-yl)-N-propyl-isophthalamic acid methyl ester (0.123 g, 0.286 mmol) in dichloromethane (1 mL) to the bottle and stir at RT for 2 h. Dilute the solution with dichloromethane (5 mL) and filter though a pad of magnesium sulfate and aluminum oxide. Wash solid with EtOAc (50 mL), concentrate and purify (silica gel chromatography, eluting with 20:80 to 30:70 EtOAc:hexanes) to give the title compound (42%).

MS (ES): m/z = 361.9 [M+H].

5-(Difluorophenyl-methyl)-N-methyl-N-propyl-isophthalamic acid

Chill a solution of 5-(difluorophenyl-methyl)-N-methyl-N-propyl-isophthalamic acid methyl ester (0.043 g, 0.119 mmol) in THF (1 mL) in an ice bath. Add 1 N lithium hydroxide (0.18 mL, 0.18 mmol) and stir at RT for 3 h. Acidify the solution to about pH = 2 and concentrate to one half of the solvent. Partition the residue between EtOAc and H_2O. Extract the aqueous layer with EtOAc (2 x 10 mL). Wash the combined organic extract with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (95%).

MS (ES): m/z = 346.2 [M+H].

Preparation 127

N-Methyl-N-propyl-5-thiazol-2-yl-isophthalamic acid

5-Iodo-isophthalic acid monomethyl ester

Dissolve 5-iodo-isophthalic acid dimethyl ester (10 g, 31.2 mmol) in methanol (90 mL) and cool to 0 °C. Add 2 N NaOH (15.6 mL) dropwise and slowly warm up to RT. Stir overnight and acidify to about pH = 3 with 5 N HCl. Extract with ethyl acetate (2 x 50 mL). Wash the combined organic layers by water, saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound as a crude residue which is used in the next step without further purification.

MS (ES): m/z = 305.0 [M-H].

5-Iodo-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve 5-iodo-isophthalic acid monomethyl ester (9.34 g, 30.5 mmol), 1-hydroxybenzotriazole hydrate (4.86 g, 36 mmol) and a solution of 1,3-dicyclohexylcarbodiimide (1 M in dichloromethane; 36 mL) in THF (70 mL). Cool to 0 °C for 15 min. Add methylpropylamine (3.69 mL, 36 mmol) and stir at RT for 12 h. Filter the solution though a filtering agent and wash with ethyl acetate, concentrate and purify (silica gel chromatography, eluting with 20:80 ethyl acetate:hexanes) to give the title compound.

N-Methyl-N-propyl-5-thiazol-2-yl-isophthalamic acid methyl ester

To a previously nitrogen-flushed vessel, add zinc dust (<10 microns, 0.196 g, 3 mmol) and 1,2-dibromoethane (0.023 mL, 0.27 mmol) to THF (0.5 mL). Heat the solution until bubbles appear. Repeat the heating twice and cool to RT. Add chlorotrimethylsilane (15 μL) and 2-bromothiazole (90 μL, 1 mmol) in THF (0.4 mL). Stir at RT for 15 min. Add 5-iodo-N-methyl-N-propyl-isophthalamic acid methyl ester (541 mg, 1.5 mmol), tetrakis(triphenylphosphine)palladium (0) (15 mg) and flush the mixture with nitrogen again before heating to reflux for 10 h. Cool to RT, concentrate and purify (silica gel chromatography, eluting with 0:100 to 40:60 ethyl acetate:hexanes) to give the title compound (95%).

MS (ES): m/z = 319.2 [M+H].

N-Methyl-N-propyl-5-thiazol-2-yl-isophthalamic acid

Dissolve N-Methyl-N-propyl-5-thiazol-2-yl-isophthalamic acid methyl ester (150 mg, 0.47 mmol) in methanol (6 mL). Add dropwise 2 N NaOH (0.3 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 by 5 N HCl and concentrate to near dryness. Dilute with ethyl acetate (20 mL) and wash the organic layer with saturated aqueous sodium chloride solution, dry (magnesium sulfate) and concentrate to give the title compound as an oil.

MS (ES): m/z = 305 [M+H].

Preparation 128

N-Methyl-5-(1-methyl-1H-imidazol-2-yl)-N-propyl-isophthalamic acid

N-Methyl-5-(1-methyl-1H-imidazol-2-yl)-N-propyl-isophthalamic acid methyl ester

Add n-butyl lithium (2.0 M in pentane, 0.78 mL, 1.55 mmol) dropwise over 30 min to a previously nitrogen-flushed, flame-dried vessel containing 1-methyl-1H-imidazole (0.12 mL, 1.5 mmol) in THF (10 mL) at –78°C, and stir for 30 min at the same temperature. Warm the solution to 0 °C and add dropwise zinc (II) chloride (1.0 M in diethyl ether, 4.5 mL, 4.5 mmol) over 10 min. Stir the mixture at the same temperature for 1 h and at RT for 30 min. Add 5-iodo-N-methyl-N-propyl-isophthalamic acid methyl ester (361 mg, 1.0 mmol) and tetrakis(triphenylphosphine)palladium (0) (12 mg) under nitrogen before heating the reaction to reflux for 20 min. Cool to RT, concentrate and purify (silica gel chromatography, eluting with 0:100 to 8:92 methanol:dichloromethane) to give the title compound.

N-Methyl-5-(1-methyl-1H-imidazol-2-yl)-N-propyl-isophthalamic acid

Dissolve N-methyl-5-(1-methyl-1H-imidazol-2-yl)-N-propyl-isophthalamic acid methyl ester (100 mg, 0.32 mmol) in methanol (10 mL). Dropwise add 1 N lithium hydroxide (0.38 mL) and stir overnight at RT. Add 2 N NaOH (0.1 mL) and stir for 48 h at RT. Acidify the mixture to about pH = 6 by DOWEX® 50WX2-100 ion exchange resin and filter. Concentrate filtrate and lyophilize (1:1 acetonitrile:water) to give the title compound.

MS (ES): m/z = 300 [M-H].

Preparation 129

5-Benzoyl-N-methyl-N-propyl-isophthalamic acid

N-Methyl-N-propyl-5-tributylstannanyl-isophthalamic acid methyl ester

Dissolve 5-iodo-N-methyl-N-propyl-isophthalamic acid methyl ester (3.0 g, 8.3 mmol), bis(tributyltin) (4.99 mL, 9.97 mmol) and trans-dichlorobis(triphenylphosphine)palladium (II) (582 mg, 0.83 mmol) in toluene (20 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen and heat the sealed mixture for 24 h at 90 °C. Cool the reaction to RT and filter though a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the title compound (66%).

5-Benzoyl-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve N-methyl-N-propyl-5-tributylstannanyl-isophthalamic acid methyl ester (480 mg, 0.8 mmol), benzoyl chloride (117 mg), tris(dibenzylideneacetone)dipalladium (0) (19.3 mg) and 2-(di-tert-butylphosphino)biphenyl (34.5 mg) in chloroform (8 mL) in a previously degassed sealed vessel. Flush the mixture with nitrogen and heat the sealed mixture overnight at 60 °C. Cool the reaction to RT and filter though a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 30:70 ethyl acetate:hexanes) to give the title compound (66%).

5-Benzoyl-N-methyl-N-propyl-isophthalamic acid

Dissolve 5-benzoyl-N-methyl-N-propyl-isophthalamic acid methyl ester (60 mg, 0.17 mmol) in methanol (4 mL). Add dropwise 1 N-lithium hydroxide (0.23 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 by 5 N HCl and concentrate to near dryness. Dilute the residue with ethyl acetate and wash with saturated aqueous sodium chloride solution, dry (magnesium sulfate) and concentrate to give the title compound (83%).

MS (ES): m/z = 324 [M-H].

Preparation 130

5-(Furan-2-carbonyl)-N-methyl-N-propyl-isophthalamic acid

5-(Furan-2-carbonyl)-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve N-methyl-N-propyl-5-tributylstannanyl-isophthalamic acid methyl ester (500 mg, 1 mmol), furan-2-carbonyl chloride (0.12 mL), tris(dibenzylideneacetone)-dipalladium (0) (19 mg) and 2-(di-tert-butylphosphino)biphenyl (35 mg) in THF (6 mL) in a previously degassed, sealed vessel. Flush the mixture with nitrogen and heat the sealed mixture overnight at 50 °C. Cool the reaction to RT and filter though a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, 0:100 to 38:62 ethyl acetate:hexanes) to give the title compound (50%).

5-(Furan-2-carbonyl)-N-methyl-N-propyl-isophthalamic acid

Dissolve 5-(furan-2-carbonyl)-N-methyl-N-propyl-isophthalamic acid methyl ester (100 mg, 0.3 mmol) in methanol (10 mL). Add dropwise 2 N NaOH (0.225 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 by 5 N HCl and concentrate to near dryness. Dilute the residue with ethyl acetate and wash by saturated aqueous sodium chloride solution, dry (magnesium sulfate) and concentrate.
MS (ES): m/z = 314.2 [M-H].

Preparation 131

5-(Difluorofuran-2-ylmethyl)-N-methyl-N-propyl-isophthalamic acid

5-(2-Furan-2-yl-[1,3]dithiolan-2-yl)-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve 5-(furan-2-carbonyl)-N-methyl-N-propyl-isophthalamic acid methyl ester (290 mg, 0.88 mmol) in dichloromethane (2 mL). Cool to 0 °C, add a solution of ethane-1,2-dithiol (0.22 mL, 2.2 mmol) and then add a solution of boron trifluoride dibutyl etherate (0.66mL, 5.2 mmol) in dichloromethane (5 mL). Warm the mixture to RT and stir overnight. Quench with water and dilute with dichloromethane. Wash the organic layer by saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 0:100 to 30:70 ethyl acetate:hexanes) to give the title compound (38%).

5-(Difluorofuran-2-yl-methyl)-N-methyl-N-propyl-isophthalamic acid methyl ester

Under nitrogen and in a plastic vessel, dissolve nitrosonium tetrafluoroborate (84.8 μg, 0.72 mmol) and pyridinium poly(hydrogen fluoride) (70% hydrogen fluoride, 30% pyridine,300 μL) in dichloromethane (2 mL) and cool to 0 °C. Add dropwise 5-(2-furan-2-yl-[1,3]dithiolan-2-yl)-N-methyl-N-propyl-isophthalamic acid methyl ester in dichloromethane (1.5 mL) to the mixture, warm up to RT and stir for 2 h. Dilute the mixture with dichloromethane (20 mL) and filter the organic liquid though a pad of aluminum oxide and magnesium sulfate mixture. Concentrate the filtrate and purify (silica gel chromatography, 1:99 to 30:70 ethyl acetate:hexanes) to give the title compound (30%).

MS (ES): m/z = 352 [M+H].

5-(Difluorofuran-2-yl-methyl)-N-methyl-N-propyl-isophthalamic acid

Dissolve 5-(difluorofuran-2-yl-methyl)-N-methyl-N-propyl-isophthalamic acid methyl ester (30 mg, 0.08 mmol) in methanol (2 mL). Add dropwise 2 N NaOH (0.06 mL) and stir overnight at RT. Acidify the mixture to about pH = 6 with 5 N HCl and concentrate to near dryness. Dilute the residue with ethyl acetate, wash with saturated aqueous sodium chloride solution, dry (magnesium sulfate) and concentrate to give the title compound (66%).

MS (ES): m/z = 335 [M-H].

Preparation 132

N-Methyl-5-(2-methylacryloyl)-N-propyl-isophthalamic acid

N-Methyl-5-(2-methylacryloyl)-N-propyl-isophthalamic acid methyl ester

Dissolve N-methyl-N-propyl-5-tributylstannanyl-isophthalamic acid methyl ester (885 mg, 168 mmol), 2-methyl-acryloyl chloride (172 mg, 1.64 mmol), tris(dibenzylideneacetone)dipalladium (46 mg, 0.05 mmol) and tricyclohexylphosphine (46 mg, 0.16 mmol)) in chloroform (15.5 mL) in a previously degassed vessel. Flush the mixture with nitrogen gas and heat the sealed mixture overnight at 60 °C. Cool to RT and filter though a filtering agent. Concentrate the filtrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the title compound.

N-Methyl-5-(2-methylacryloyl)-N-propyl-isophthalamic acid

Dissolve N-methyl-5-(2-methylacryloyl)-N-propyl-isophthalamic acid methyl ester (50 mg, 0.16 mmol) in methanol (3 mL). Add 2 N NaOH (0.12 mL) and stir overnight at RT. Add 2 N NaOH (0.05 mL) and stir for an additional 3 h. Acidify the mixture to about pH = 6 using DOWEX® 50WX2-100 ion exchange resin and filter. Concentrate filtrate to give the title compound which is used in the next step without further purification.

MS (ES): m/z = 288 [M-H].

Preparation 133

5-Isobutyryl-N-methyl-N-propyl-isophthalamic acid

5-(1-Hydroxy-2-methyl-propyl)-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve N-methyl-5-(2-methylacryloyl)-N-propyl-isophthalamic acid methyl ester (80 mg, 0.26 mmol) in ethyl acetate (25 mL) under nitrogen. Add Raney® nickel (100 mg) and hydrogenate the reaction for 2 h at RT under an atmosphere of hydrogen gas (40 psi). Filter the reaction and concentrate to give the crude title product.

MS (ES): m/z = 308 [M+H].

5-Isobutyryl-N-methyl-N-propyl-isophthalamic acid methyl ester

Dissolve 5-(1-hydroxy-2-methyl-propyl)-N-methyl-N-propyl-isophthalamic acid methyl ester (70 mg, 0.23 mmol) in dichloromethane (3 mL) and add Dess-Martin periodinane (174 mg, 0.41 mmol) at RT. Stir the mixture overnight and quench with 10% aqueous sodium bisulfite solution. Extract the organic layer, wash with saturated aqueous sodium chloride solution, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 30:70 ethyl acetate:hexanes) to give the title compound.

5-Isobutyryl-N-methyl-N-propyl-isophthalamic acid

Dissolve 5-isobutyryl-N-methyl-N-propyl-isophthalamic acid methyl ester (50 mg, 0.16 mmol) in methanol (3 mL) and add dropwise 2 N NaOH (0.16 mL). Stir the mixture at RT for 6 h, store overnight at 4 °C and acidify to about pH = 6 by 5 N HCl. Concentrate to near dryness and dilute the residue with ethyl acetate. Wash with saturated aqueous sodium chloride solution and extract the organic layer, dry (magnesium sulfate) and concentrate to give the title compound.
MS (ES): *m/z* = 289[M-H].

Preparation 134

5-Nitro-N,N-dipropyl-isophthalamic acid

5-Nitro-N,N-dipropyl-isophthalamic acid methyl ester

Dissolve commercially available monomethyl 5-nitroisophthalate (3.000 g, 14.07 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.238 g, 16.89 mmol), 1-hydroxybenzotriazole hydrate (2.587 g, 16.89 mmol) and 4-dimethylaminopyridine (0.172 g, 1.407 mmol) and triethylamine (5.885 mL, 42.22 mmol) in dichloromethane (309 mL) and stir the mixture at RT for 0.5 h. Add dipropylamine (2.026 mL, 14.78 mmol) and triethylamine (5.885 mL, 42.22 mmol) and stir the mixture overnight. Concentrate and redissolve the residue in ethyl acetate and wash with two portions each of 5% aqueous potassium hydrogen sulfate solution, 5% aqueous sodium bicarbonate solution, saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (3.885 g, 90%).
MS (ES): *m/z* = 309.1 [M+H].

5-Nitro-N,N-dipropyl-isophthalamic acid

Dissolve 5-nitro-N,N-dipropyl-isophthalamic acid methyl ester (1.000 g, 3.243 mmol) and lithium hydroxide (0.089 g, 3.730 mmol) in a mixture of THF (3.16 mL), water (1.58 mL) and methanol (1.58 mL). Stir the mixture at RT until the starting material is consumed. Concentrate and acidify with 1 N HCl. Extract with ethyl acetate, dry (magnesium sulfate) and concentrate to give the title compound (0.874 g, 92%).
MS (ES): *m/z* = 293.1 [M-H].

Preparation 135

5-Acetyl-N-methyl-N-propyl-isophthalamic acid

5-Formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Treat a solution 5-hydroxymethyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (5.79 g, 20.7 mmol) in dichloromethane (50 mL) at –78 °C with oxalyly chloride (1.99 mL, 22.8 mmol), DMSO (3.5 mL, 49.5 mmol), and triethylamine (8.6 mL, 62.1 mmol). Stir at –78 °C for 30 min, warm to RT and stir for 1 h. Quench with ice and extract with dichloromethane (100 mL). Wash with saturated aqueous $NaHCO_3$, saturated aqueous sodium chloride, dry (magnesium sulfate) concentrate and purify (silica gel chromatography, eluting with 40:60 to 50:50 EtOAc:hexanes) to give the title compound (4.53 g, 78%).

MS (ES): m/z = 278.3 [M+H].

5-(1-Hydroxyethyl)-N-methyl-N-propyl-isophthalamic acid ethyl ester

Treat a solution of 5-formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (400 mg, 1.44 mmol) in THF (10 mL) at 0 °C with methylmagnesium bromide (3.0 M in diethyl ether, 0.58 mL, 1.73 mmol). Stir at 0 °C for 1 h and quench with saturated aqueous ammonium chloride solution. Extract with EtOAc (100 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 40:60 to 70:30 EtOAc:hexanes) to give the title compound (250 mg, 59%).

MS (ES): m/z = 293.9 [M+H].

5-Acetyl-N-methyl-N-propyl-isophthalamic acid ethyl ester

Treat a solution of 5-(1-hydroxyethyl)-N-methyl-N-propyl-isophthalamic acid ethyl ester (250 mg, 0.85 mmol) in dichloromethane (10 mL) with Dess-Martin periodinane (470 mg, 1.11 mmol). Stir at RT for 2.5 h, quench with 10% aqueous sodium sulfate, extract with EtOAc (50 mL). Wash with 10% aqueous sodium sulfate solution, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 50:50 EtOAc:hexanes) to give the title compound (196 mg, 78%).

MS (ES): m/z = 291.9 [M+H].

5-Acetyl-N-methyl-N-propyl-isophthalamic acid

Treat a solution of 5-acetyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (196 mg, 0.67 mmol) in ethanol (7 mL) at RT with 2 N NaOH (0.5 mL, 1.0 mmol) for 12 h. Acidify to about pH = 3 using 1 N HCl. Extract with EtOAc (50 mL), dry (magnesium sulfate) and concentrate to give the title compound (179 mg, 95%).
MS (ES): m/z = 263.9 [M+H].

Preparation 136

N-Methyl-N-propyl-5-(2,2,2-trifluoro-acetyl)-isophthalamic acid

N-Methyl-N-propyl-5-(2,2,2-trifluoro-1-hydroxyethyl)-isophthalamic acid

N-Methyl-N-propyl-5-(2,2,2-trifluoro-1-hydroxyethyl)-isophthalamic acid ethyl ester

Treat a solution of 5-formyl-N-methyl-N-propyl-isophthalamic acid ethyl ester (500 mg, 1.8 mmol) in THF (10 mL) at 0 °C with trimethyl(trifluoromethyl)silane (0.5 M in THF, 5.4 mL, 2.70 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 2.7 mL, 2.70 mmol). Stir at 0 °C for 2 h and quench with saturated aqueous $NaHCO_3$. Extract with EtOAc (100 mL), dry (magnesium sulfate) and concentrate to give the crude title product which is used in the next step without further purification.
MS (ES): m/z = 347.9 [M+H].

N-Methyl-N-propyl-5-(2,2,2-trifluoroacetyl)-isophthalamic acid ethyl ester

Treat a solution of N-methyl-N-propyl-5-(2,2,2-trifluoro-1-hydroxyethyl)-isophthalamic acid ethyl ester (1.8 mmol) in dichloromethane (20 mL) with Dess-Martin reagent at RT for 2 h. Quench with 10% aqueous sodium sulfite and extract with EtOAc (100 mL). Wash the organic layer with 10% aqueous sodium sulfite, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 60:40 EtOAc:hexanes) to give the title compound (330 mg) which is contaminated with recovered N-methyl-N-propyl-5-(2,2,2-trifluoro-1-hydroxyethyl)-isophthalamic acid ethyl ester in a ratio of about 4:1).
MS (ES): m/z = 346.3 [M+H].

N-Methyl-N-propyl-5-(2,2,2-trifluoroacetyl)-isophthalamic acid

N-Methyl-N-propyl-5-(2,2,2-trifluoro-1-hydroxyethyl)-isophthalamic acid

Treat a solution of a mixture of N-methyl-N-propyl-5-(2,2,2-trifluoroacetyl)-isophthalamic acid (330 mg, 0.96 mmol) and N-methyl-N-propyl-5-(2,2,2-trifluoro-1-hydroxyethyl)-isophthalamic acid in a ratio of about 4:1 in ethanol (12 mL) with 2 N NaOH (0.72 mL, 1.43 mmol). Stir at RT for 12 h, add more 2 N NaOH (1.5 eq.), and stir overnight at RT. Acidify to about pH = 3 with 1 N HCl. Extract with EtOAc (50 mL), dry (magnesium sulfate) and concentrate to give a mixture of the two title products, N-methyl-N-propyl-5-(2,2,2-trifluoroacetyl)-isophthalamic acid (MS (ES): m/z = 316.1 [M-H] and N-methyl-N-propyl-5-(2,2,2-trifluoro-1-hydroxyethyl)-isophthalamic acid (MS (ES): m/z = 318.1 [M-H]) in a ratio of about 4:1 respectively.

Preparation 137

5-Difluoromethoxy-N-methyl-N-propyl-isophthalamic acid

5-Difluoromethoxy-isophthalic acid dimethyl ester

React 5-hydroxy-isophthalic acid dimethyl ester (5.88 g, 28 mmol), methyl 2-chloro-2,2-difluoroacetate (5.9 mL, 56 mmol), cesium carbonate (18.2 g, 56 mmol) in methyl ethyl ketone at reflux for 2 days. Cool to RT, filter though a filtering agent, wash with EtOAc, concentrate and purify (silica gel chromatography, eluting with 10:90 to 30:70 EtOAc:hexanes) to give the title compound (2.7 g, 37%).
MS (ES): m/z = 261.2 [M+H].

5-Difluoromethoxy-isophthalic acid monomethyl ester

Treat a solution of 5-difluoromethoxy-isophthalic acid dimethyl ester (2.7 g, 10.4 mmol) in methanol (35 mL) with 2 N NaOH (5.2 mL, 10.4 mmol) at RT for 12 h. Acidify to about pH = 3 using 5 N HCl. Extract with EtOAc, wash the organic layer with water, saturated aqueous sodium chloride, dry (sodium sulfate) and concentrate to give the crude title product which isused in the next step without further purification.
MS (ES): m/z = 245.1 [M-H].

5-Difluoromethoxy-N-methyl-N-propyl-isophthalamic acid methyl ester

Treat a solution containing crude 5-difluoromethoxy-isophthalic acid monomethyl ester (2.5 g, 10 mmol) in THF (20 mL) at RT with 1-hydroxtbenzotriazole hydrate (1.62 g, 12 mmol), 1,3-dicyclohexylcarbodiimide (12 mL, 1 N, 12 mmol), and n-

methylpropylamine (1.23 mL, 12 mmol). Stir at RT overnight, filter through a filtering agent, wash with 1:1 EtOAc:hexanes (50 mL). Concentrate the combined filtrates and purify (silica gel chromatography, eluting with 0:100 to 30:70 EtOAc:hexanes) to give the title compound as a solid (1.6 g, 53%).

MS (ES): m/z = 302 [M+H].

5-Difluoromethoxy-N-methyl-N-propyl-isophthalamic acid

Treat a solution of 5-difluoromethoxy-N-methyl-N-propyl-isophthalamic acid methyl ester (1.6 g, 5.3 mmol) in methanol (30 mL) with 2 N NaOH (4 mL, 8.0 mmol). Stir at RT overnight and acidify to about pH = 4 using 1 N HCl. Extract with EtOAc (150 mL), wash the organic layer with saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound which is used in the next step without further purification.

MS (ES): m/z = 286.1 [M-H].

Preparation 138

N-Methyl-N-propyl-5-pyridin-4-yl-isophthalamic acid

5-Iodo-N-methyl-N-propyl-isophthalamic acid benzyl ester

Add benzyl chloroformate (5.96 mL, 41.77 mmol) to a solution of 5-iodo-N-methyl-N-propyl-isophthalamic acid (14.5 g, 41.77 mmol), triethylamine (6.4 mL, 45.95 mmol) and 4-dimethylaminopyridine (2.55 g, 20.88 mmol) in dichloromethane (125 mL) at 0 °C and at RT for 40 h. Wash the solution twice with a saturated aqueous solution of $NaHCO_3$, 5% aqueous solution of potassium hydrogen sulfate, saturated aqueous sodium chloride, dry (magnesium sulfate), and concentrate. Dissolve the crude in dichloromethane, wash with a 0.5 N NaOH solution, H_2O, saturated aqueous sodium chloride, dry (magnesium sulfate) and concentrate to give the title compound (6 g, 33%).

MS (ES): m/z = 438.1 [M+H].

N-Methyl-N-propyl-5-pyridin-4-yl-isophthalamic acid benzyl ester

Add pyridine-4-boronic acid (2.361 g, 19.21 mmol) and 2 N sodium carbonate (19.21 mL, 38.42 mmol) to a solution of 5-iodo-N-methyl-N-propyl-isophthalamic acid benzyl ester (6.000 g, 13.72 mmol)in ethylene glycol dimethyl ether (206 mL) under

nitrogen at RT. Add tetrakis(triphenylphosphine)palladium (0) (0.634 g, 0.549 mmol) and reflux for 20 h. Cool to RT and concentrate. Add EtOAc, separate the organic layer and extract the aqueous layer with EtOAc (4x). Wash the combined organic layers with H_2O, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with EtOAc) to give the title compound (56%).
MS (ES): m/z = 389.2 [M+H].

N-Methyl-N-propyl-5-pyridin-4-yl-isophthalamic acid

Stir a mixture of N-methyl-N-propyl-5-pyridin-4-yl-isophthalamic acid benzyl ester (1.900 g, 4.891 mmol), 10% palladium on carbon (0.208 g) in MeOH (50 mL) under an atmosphere of hydrogen gas (1 atm) for 0.5 h. Filter through a filtering agent and concentrate to give the title compound (quantitative yield).
MS (ES): m/z = 299.2 [M+H].

Preparation 139

6-Fluoro-5-(methanesulfonyl-methylamino)-N-methyl-N-propyl-isophthalamic acid

5-Bromo-2-fluorophenylamine

Dissolve tin (II) chloride hydrate (86.2 g, 455 mmol), 4-bromo-2-fluoro-1-nitro-benzene (20.0 g, 90.9 mmol) and water (16.4 mL, 909 mmol) in ethanol (475 mL). Reflux the mixture for 6 h. Cool to RT and concentrate to a minimal volume. Add ethyl acetate (400 mL) and saturated aqueous sodium bicarbonate solution (1.6 L) to the residue and stir vigorously for 1 h. Filter through a filtering agent and wash with ethyl acetate (2 L). Separate the layers and extract the aqueous layer with ethyl acetate (1 L). Combine the organic layers, wash with saturated aqueous sodium chloride (500 mL), dry (magnesium sulfate) and concentrate to give the title compound as a solid (16.8 g, 97%).
MS (ES): m/z = 190 [M+].

Dibenzyl-(5-bromo-2-fluorophenyl)-amine

Stir a slurry of 4-bromo-2-fluorophenylamine (15.0 g, 78.9 mmol), potassium carbonate (43.6 g, 316 mmol) and benzyl bromide (28.2 mL, 237 mmol) in DMF (75 mL) at 100 °C for 18 h. Cool to RT and dilute with dichloromethane (200 mL). Filter the slurry and wash with dichloromethane. Wash the filtrate with water (500 mL) and 1 N

lithium chloride (250 mL). Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 5:95 to 35:65 dichloromethane:hexanes) to give the title compound as a solid (26.2 g, 90%).

MS (ES): *m/z* = 372 [M+2].

5-Bromo-3-dibenzylamino-2-fluorobenzoic acid

Add dropwise a solution of dibenzyl-(5-bromo-2-fluorophenyl)-amine (4.00 g, 10.8 mmol) in THF (12 mL) to a solution of lithium diisopropylamide, freshly prepared by adding n-butyllithium (1.6 M in hexanes, 7.09 mL, 11.3 mmol) to diisopropylamine (1.74 mL, 12.4 mmol) in THF (25 mL) at –78 °C. Stir the resulting yellow solution at –78 C for 45 min. Pour into a dry ice slurry containing about 100 g in dry THF (40 mL). Stir the solution until it reaches RT. Concentrate the solution and dissolve the residue in 10% aqueous potassium hydroxide solution (40 mL) and extract with diethyl ether (70 mL). Acidify the aqueous layer to about pH = 3 with concentrated HCl. Extract the aqueous layer with diethyl ether (2 x 200 mL). Combine the organic layers and wash with water (150 mL), dry (magnesium sulfate) and concentrate to give the title compound as a solid (1.81 g, 40%).

MS (ES): *m/z* = 416 [M+2].

5-Bromo-3-dibenzylamino-2-fluorobenzoic acid ethyl ester

Dissolve 5-bromo-3-dibenzylamino-2-fluorobenzoic acid (1.53 g, 3.69 mmol) in ethanol (40 mL). Add concentrated sulfuric acid (0.2 mL) as a catalyst and heat to at reflux for 1 day. Cool to RT and concentrate. Dissolve the residue in diethyl ether (30 mL) and wash with 10% aqueous potassium carbonate solution (10 mL) and water (10 mL). Dry (magnesium sulfate) and concentrate to give the title compound as an oil (1.50 g, 92%).

MS (ES): *m/z* = 442 [M].

5-Dibenzylamino-4-fluoro-isophthalic acid 3-ethyl ester

Combine 5-bromo-3-dibenzylamino-2-fluorobenzoic acid ethyl ester (4.74 g, 10.7 mmol), palladium (II) acetate (0.72 g, 3.20 mmol), 1,4-bis(diphenylphosphino)butane (2.84 g, 6.66 mmol), triethylamine (7.90 mL, 56.7 mmol), DMSO (150 mL), tert-butyl

alcohol (100 mL), and water (0.50 mL, 27.8 mmol). Place mixture in a container pressurized to 100 psi with carbon monoxide and heat at 80 °C for 24 h. Filter the reaction mixture over a pad of filtering agent. Pour the filtrate into water (500 mL), acidify with 5 N HCl and extract (2 x 500 mL) with ethyl acetate. Dry (magnesium sulfate), concenetrate and purify (silica gel chromatography, eluting with 4:96 methanol:dichloromethane) to give the title compound as a solid (2.40 g, 55%).
MS (ES): m/z = 408 [M+H].

5-Dibenzylamino-6-fluoro-N-methyl-N-propyl-isophthalamic acid ethyl ester

Dissolve the 1-hydroxybenzotriazole hydrate (139 mg, 1.03 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (197 mg, 1.03 mmol) and 5-dibenzylamino-4-fluoro-isophthalic acid 3-ethyl ester (381 mg, 0.934 mmol) in dichloromethane (10.0 mL). Stir for 30 min. Add methylpropyl amine (68.3 mg, 0.93 mmol) to the reaction mixture. Stir the reaction for 4 h. Add 10% aqueous potassium carbonate solution (10 mL). Extract with dichloromethane (2 x 50 mL). Combine the organic layers, wash with water (20 mL), saturated aqueous sodium chloride (20 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 40:60 ethyl acetate:hexanes) to give the title compound (279 mg, 65%).
MS (ES): m/z = 463 [M+H].

5-Amino-6-fluoro-N-methyl-N-propyl-isophthalamic acid ethyl ester

Dissolve 5-dibenzylamino-6-fluoro-N-methyl-N-propyl-isophthalamic acid ethyl ester (275 mg, 0.595 mmol) in ethanol (6 mL). Add 10% Pd/C to the solution (50 mg). Stir the black slurry under a balloon containing hydrogen gas for 2.5 days. Filter the slurry through a pad of filtering agent and wash with ethanol. Concentrate the filtrate to give the title compound as a crude product.
MS (ES): m/z = 283 [M+H].

6-Fluoro-5-methanesulfonylamino-N-methyl-N-propyl-isophthalamic acid ethyl ester

Dissolve 5-amino-6-fluoro-N-methyl-N-propyl-isophthalamic acid ethyl ester (0.162 g, 0.58 mmol) in dichloromethane (1.5 mL). Cool to 0 °C. Add pyridine (51.2 µL, 0.63 mmol) and methanesulfonyl chloride (44.5 µL, 0.58 mmol) to the solution.

Allow the reaction to warm to RT and stir for 2 days. Quench with water (10 mL) and extract with dichloromethane (2 x 30 mL). Combine the organic layers and wash with saturated aqueous sodium chloride (20 mL), dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 40:60 ethyl acetate:dichloromethane) to give the title compound as a solid (157 mg, 76%).

MS (ES): $m/z = 361$ [M+H].

6-Fluoro-5-(methanesulfonyl-methylamino)-N-methyl-N-propyl-isophthalamic acid ethyl ester

Dissolve 6-fluoro-5-methanesulfonylamino-N-methyl-N-propyl-isophthalamic acid ethyl ester (0.160 g, 0.444 mmol) in DMF (1.0 mL). Add potassium carbonate (44.4 mg, 0.32 mmol), iodomethane (41.5 µL, 0.67 mmol) and tetrabutylammonium bromide (14.3 mg, 0.04 mmol) to the solution. Stir the resulting slurry at RT for 16 h. Quench with saturated aqueous sodium sulfate solution (10 mL) and extract with ethyl acetate (3 x 30 mL). Combine the organic layers and dry (magnesium sulfate). Azeotrope the residue with xylenes to remove residual DMF. Purify (silica gel chromatography, eluting with 40:60 ethyl acetate:dichloromethane) to give the title compound as a solid (111 mg, 67%).

MS (ES): $m/z = 375$ [M+H].

6-Fluoro-5-(methanesulfonyl-methylamino)-N-methyl-N-propyl-isophthalamic acid

Dissolve the 6-fluoro-5-(methanesulfonyl-methyl-amino)-N-methyl-N-propyl-isophthalamic acid ethyl ester (110 mg, 0.30 mmol) in THF (7.5 mL). Add 1 N sodium hydroxide solution (1.48 mL, 1.48 mmol) and stir the resulting biphasic mixture vigorously for 4 h. Acidify with 1 N HCl (1.55 mL, 1.55 mmol) and concentrate the solution to a volume of about 3 mL. Extract the solution with diethyl ether (2 x 20 mL). Combine the organic layers, dry (magnesium sulfate) and concentrate to give the title compound as a solid (95.2 mg, 93%).

MS (ES): m/z = 347 [M+H].

Preparation 140

5-(Methyl-propylcarbamoyl)-1-oxy-nicotinic acid

5-(Methyl-propylcarbamoyl)-1-oxy-nicotinic acid methyl ester

Mix 5-(methyl-propylcarbamoyl)-nicotinic acid methyl ester (396 mg, 1.67 mmol) and 3-chloroperoxybenzoic acid (1.2g, 50-85%) in dichloromethane (50 mL) and stir over the weekend. Dilute with dichloromethane (50 mL) and wash with 5% aqueous sodium bicarbonate solution (20 mL), dry (sodium sulfate), and concentrate to give the crude title compound which is used in the next step without further purification.

MS (ES): m/z = 253 [M+H].

5-(Methyl-propylcarbamoyl)-1-oxy-nicotinic acid

Dissolve crude 5-(methyl-propylcarbamoyl)-1-oxy-nicotinic acid methyl ester (0.72 mmol) in 1 N sodium hydroxide (1.4 mL) and methanol (2 mL). Stir at RT overnight. Concentrate organic and redissolve the residue in water (15 mL). Wash with dichloromethane (3 x 10 mL), acidify with 1 N HCl to about pH = 2 and concentrate to give the crude title product which is directly in the next step.

MS (ES): m/z = 239 [M+H].

Preparation 141

2-Chloro-5-(methyl-propylcarbamoyl)-nicotinic acid

2-Chloro-5-(methyl-propylcarbamoyl)-nicotinic acid methyl ester

Stir 5-(methyl-propylcarbamoyl)-1-oxy-nicotinic acid methyl ester (353 mg, 1.40 mmol) in phosphorus oxychloride (2 mL,) at 100 °C for 1 h. Cool to RT and quench with saturated aqueous sodium acetate (50 mL) and ethyl acetate (100 mL). Separate the organic layer, wash with water (50 mL), dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with ethyl acetate and hexanes) to give the title compound (208 mg, 55%).

MS (ES): $m/z = 271$ [M+H].

2-Chloro-5-(methyl-propylcarbamoyl)-nicotinic acid

Dissolve 2-chloro-5-(methyl-propylcarbamoyl)-nicotinic acid methyl ester (96 mg, 0.35 mmol) in 1 N sodium hydroxide (0.71 mL, 0.71 mmol) and methanol (2 mL). Stir at RT for 2 h. Concentrate organic and redissolve the residue in water (15 mL). Wash with dichloromethane (3 x 10 mL), acidify the aqueous layer with 1 N HCl to about pH = 2. Extract with dichloromethane, dry (sodium sulfate) and concentrate to give the crude title product which is used in the next step without further purification.

MS (ES): $m/z = 257$ [M+H].

Preparation 142

2-Dipropylcarbamoyl-isonicotinic acid

4-Chloropyridine-2-carboxylic acid dipropylamide

Stir a solution of 4-chloro-2-pyridine carboxylic acid (1.0 g, 6.3 mmol), 1-hydroxybenzotriazole (850 mg, 6.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.21 g, 6.3 mmol), dipropyl amine (862μL, 6.3 mmol), and triethylamine (1.75 mL, 12.6 mmol) in dichloromethane (63 mL) at RT over the weekend. Wash the solution with 0.1 N citric acid (2 x 50 mL), saturated aqueous sodium bicarbonate (50 mL), saturated aqueous sodium chloride (50 mL), dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 10:90 to 20:80 ethyl acetate:hexanes)to give the title compound (1.02 g, 67%).

2-Dipropylcarbamoyl-isonicotinic acid

Heat a mixture of 4-chloropyridine-2-carboxylic acid dipropylamide (1.02 g, 4.2 mmol), palladium (II) acetate (11.3 mg, 0.05 mmol), triethylamine (1.0 mL, 7.1 mmol), 1,1'-bis(3,5-dimethylphenylphosphino)ferrocene (138 mg, 0.55 mmol), DMF (35 mL) and water (5 mL) at 110 °C under an atmosphere of carbon monoxide (200 psi) overnight. Filter the reaction, concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 methanol:chloroform) to give the title compound (75 mg, 7%).
MS (ES): $m/z = 251$ [M+H].

Preparation 143

5-(Methyl-propylcarbamoyl)-nicotinic acid

5-(Methyl-propylcarbamoyl)-nicotinic acid

Add a solution of pyridine-3,5-dicarboxylic acid (220 mg, 1.32 mmol), diisopropylethylamine (918 µL, 5.28 mmol), and DMF (1.5 mL) in dichloromethane (10 mL) to 2-chlorotritylchloride resin (1.0g, 1.1 mmol) in a peptide synthesis vessel and mix for 3 h. Filter and wash the resin with a 17:2:1 mixture of dichloromethane:methanol:diisopropylethylamine, followed by dichloromethane. Add a solution of methylpropylamine (225 µL, 2.2 mmol), and benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate (1.14 g, 2.2 mmol) in dichloromethane (10 mL) to the resin and mix for 1 h. Filter and wash the resin with dichloromethane (2 x 10 mL). Add a solution of 5% trifluoroacetic acid in dichloromethane (10 mL) to the resin and let stand for 10 min. Filter the resin and wash with dichloromethane (2 x 10 mL). Combine the filtrates and concentrate to give the title compound (110 mg, 50%).
MS (ES): $m/z = 223$ [M+H].

Preparation 144

4-Dipropylcarbamoyl-pyridine-2-carboxylic acid

2-chloro-N,N-dipropylisonicotinamide

Stir a solution of 2-chloroisonicotinic acid (1.0 g, 6.3 mmol), 1-hydroxybenzotriazole (850 mg, 6.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.21 g, 6.3 mmol), dipropyl amine (862 µL, 6.3 mmol), and triethylamine (1.75 mL, 12.6 mmol) in dichloromethane (63 mL) at RT over the

weekend. Wash the solution with 0.1 N citric acid (2 x 50 mL), saturated aqueous sodium bicarbonate (50 mL), saturated aqueous sodium chloride (50 mL), dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 10:90 to 20:80 ethyl acetate:hexanes) to give the title compound (1.16 g, 76%).

MS (ES): $m/z = 241$ [M+H].

4-Dipropylcarbamoyl-pyridine-2-carboxylic acid

Heat a mixture of 2-chloro-N,N-dipropylisonicotinamide (0.91 g, 3.8 mmol), palladium (II) acetate (13.2 mg), triethylamine (1.0 mL, 7.1 mmol), 1,1'-bis(3,5-dimethylphenylphosphino)ferrocene (161 mg, 0.64 mmol), DMF (35 mL) and water (5 mL) at 110 °C under an atmosphere of carbon monoxide (200 psi) overnight. Filter the reaction, concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 methanol:chloroform) to give the title compound (486 mg, 51%).

MS (ES): $m/z = 251.1$ [M+H].

Preparation 145

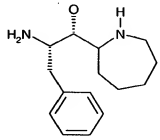
3-(Methanesulfonyl-methylamino)-benzoic acid

Prepare the title compound starting from ethyl 3-aminobenzoate according to the procedure described in WO 00/55153.

MS (ES): $m/z = 228.1$ [M-H].

Preparation 146

2-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-homopiperidine



(S)-2-Dibenzylamino-3-phenyl-propionaldehyde

Dissolve (S)-2-Dibenzylamino-3-phenyl-propan-1-ol (5.00 g, 15.1 mmol) in dimethyl sulfoxide (19 mL) and cool in an ice bath. Add triethylamine (12 mL, 192

mmol) followed by sulfur trioxide-pyridine complex (4.8 g, 30.3 mmol), stir 30 minutes then slowly add water (7 mL). Dilute with ethyl acetate and wash with 5% citric acid (3X), saturated sodium chloride, dry with magnesium sulfate and evaporate to give a light yellow residue (4.9 g, 100%). MS (ESI) *m/z* 330.2 (M+H).

(2S,3S)-2-Dibenzylamino-4-nitro-1-phenyl-oct-7-en-3-ol

Cool to –10°C a well stirred mixture of O-Allyl-N-(9-anthracenylmethyl)-cinchonidinium bromide (0.480 g, 0.8 mmol), potassium fluoride (3 gr, 51 mmol), THF (150mL) and 5-Nitro-pent-1-ene (2.34 g, 20 mmol) and treat with a solution of (S)-2-Dibenzylamino-3-phenyl-propionaldehyde (2.640 gr, 8 mmol). Allow mixture to warm to RT and stir for two days. Concentrate under reduced pressure. Purify on silica gel with hexane/ethyl ether mixtures to give a mixture of two products (2.7 g, 75%). MS (ESI) *m/z* 445.2 (M+H).

(2S,3R)-4-Amino-2-dibenzylamino-1-phenyl-oct-7-en-3-ol

Add powdered Zn (1.56 g, 24 mmol) portionwise at 0-5 °C to a stirred suspension of the (2S,3S)-2-Dibenzylamino-4-nitro-1-phenyl-oct-7-en-3-ol mixture (2.7 g, 6 mmol) in a mixture of ethanol (20 mL) and HCl conc. (20 mL). Stir for 1 h. Filter the reaction mixture and concentrate the filtrate under reduced pressure. Dilute residue with water and add concentrated ammonium hydroxide. Extract with dichloromethane. Wash the organic layer with water, dry (magnesium sulfate), and concentrate under reduced pressure to give 1.5 g of the mixture of amines (60%). MS (ESI) *m/z* 415.3 (M+H).

N-[1-((1R,2S)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl)-pent-4-enyl]-acrylamide

Add sodium carbonate (0.324 g, 3.96 mmol) and acryloyl chloride (356 mg, 3.96 mmol) to a solution of (2S,3R)-4-Amino-2-dibenzylamino-1-phenyl-oct-7-en-3-ol (1.5 g, 3.6 mmol) in dichloromethane. Stir the reaction overnight. Concentrate under reduced pressure. Purify on silica gel with hexane/ethyl acetate mixtures to give a mixture of two products (0.8 g, 48%). MS (ESI) *m/z* 469.3 (M+H).

7-((1R,2S)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl)-1,5,6,7-tetrahydro-azepin-2-one

Dissolve N-[1-((1R,2S)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl)-pent-4-enyl]-acrylamide (0.5 g, 1.06 mmol) in dichloromethane (50 mL) under nitrogen atmosphere and add Grubb´s second generation catalyst (20% mol). Stir the reaction at 50ºC for one day. Concentrate under reduced pressure. Purify on silica gel with hexane/ethyl acetate mixtures to give a mixture of two products. (0, 210 g, 45%) that may be separated using HPLC-MS (19x300 mm, 7µm, C-18 column; flow rate = 20 mL/min; mobile phase gradient 5%-95% over 26 minutes; Solvent A: acetonitrile; Solvent B: 0.1% trifluoroacetic acid in water).

Isomer 1 (MS (ESI) *m/z* 441.3 (M+H)) has a retention time of: 3.21 min and isomer B (MS (ESI) *m/z* 441.3 (M+H)) has a retention time of: 3.41 min using the following conditions:

Column: Waters, XTerra MS C_{18}, 3.5µm, 2.1 mm i.d. × 50 mm.

1. Mobile Phase

   A: 0.2 % Formic/H_2O [pH 2.2]

   B: 0.2 % Formic/ACN

2. Gradient profile:

Time	Buffer	
(min)	A(%)	B(%)
0	95	5
5.00	5	95
6.00	5	95
6.05	95	5

(1R,2S)-1-homopiperidin-2-yl-2-dibenzylamino-3-phenyl-propan-1-ol (Isomer 1)

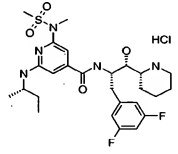
Dissolve 7-((1R,2S)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl)-1,5,6,7-tetrahydro-azepin-2-one (Isomer 1) (40 mg, 0.09 mmol) in THF (5mL) and add BH_3SMe_2 (2 M in diethyl ether, 0.14 mL, 0.27 mmol). Stir the reaction at 50°C for 3 hour. Add saturated aqueous citric acid (10 mL). Extract aqueous twice with ethyl acetate, combine organics and wash with saturated sodium chloride, dry (magnesium sulfate) and concentrate under reduced pressure. Add 20% palladium hydroxide on carbon (90 mg) and methanol (10 mL) and stir under 1 atmosphere of hydrogen overnight. Filter and evaporate to give a foam. Purify the product using a SCX column to give a thick residue (0.007 g, 40%). MS (ESI) *m/z* 249.19 (M+H).

(1R,2S)-1-Homopiperidin-2-yl-2-dibenzylamino-3-phenyl-propan-1-ol (Isomer 2)

This product may be prepared as described for (Isomer 2) beginning with 7-((1R,2S)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl)-1,5,6,7-tetrahydro-azepin-2-one (Isomer 2). MS (ESI) *m/z* 249.19 (M+H).

EXAMPLE 1

2-(S)-sec-Butylamino-N-[1-(S)-(3,5-difluorobenzyl)-2-(R)-hydroxy-2-(R)-piperidin-2-yl-ethyl]-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride



2-(R)-[2-(S)-{[2-(S)-sec-Butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester

Cool a solution of 2-(R)-[2-(S)-amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester (0.096 g, 0.258 mmol) and 2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid (0.0856 g, 0.284

mmol) in dichloromethane (2 mL) in an ice bath. Add 4-methylmorpholine (0.17 mL, 1.55 mmol) and n-propylphosphonic anhydride (0.227 mL, 0.387 mmol, 50 wt % in ethyl acetate). Stir 30 min, warm to RT and stir 30 min. Add water (3 mL) and ethyl acetate (20 mL). Wash with 5% aqueous citric acid, water, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with dichloromethane and ethyl acetate) to give the title compound as a solid (0.13 g, 78%).

MS (ES): *m/z* = 654.4 [M+H].

2-(S)-sec-Butylamino-N-[1-(S)-(3,5-difluorobenzyl)-2-(R)-hydroxy-2-(R)-piperidin-2-yl-ethyl]-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride

Cool a solution of 2-(R)-[2-(S)-{[2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester (0.082 g, 0.125 mmol) in dichloromethane (3 mL) in an ice bath. Add 4 M hydrogen chloride in 1,4-dioxane (6 mL), warm to RT, stir 1 h and concentrate to give the title compound as a foam (0.08 g, 100%).

MS (ES): *m/z* = 554.2 [M+H].

The compounds of EXAMPLES 2-7 may be prepared essentially as described in EXAMPLE 1.

EX	Compound	MS [M+H]
2	N-(1-(S)-Benzyl-2-(R)-hydroxy-2-piperidin-2-(R)-ylethyl)-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride	518.2
3	2-(S)-sec-Butylamino-N-[1-(S)-(3,5-difluorobenzyl)-2-(S)-hydroxy-2-pyrrolidin-2-(R)-ylethyl]-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride	540.4
4	N-(1-(S)-Benzyl-2-(R)-hydroxy-2-(R)-pyrrolidin-2-ylethyl)-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride	504.2
5	N-[1-(S)-Benzyl-2-(R)-(4-(S)-fluoropyrrolidin-2-yl)-2-(R)-hydroxyethyl]-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide bishydrochloride	522.2
6	N-[1-(S)-Benzyl-2-(R)-(4-(R)-fluoropyrrolidin-2-yl)-2-(R)-hydroxyethyl]-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-	522.2

	isonicotinamide bishydrochloride	
7	N-[(1S,2R)-1-Benzyl-2-((R)-4,4-difluoropyrrolidin-2-yl)-2-hydroxyethyl]-2-((S)-sec-butylamino)-6-(methanesulfonyl-methylamino)-isonicotinamide bishydrochloride	540.3

EXAMPLE 8

N-[1-(S)-Benzyl-2-hydroxy-2-(4-methyl-3-oxopiperazin-2-yl)ethyl]-2-(S)-sec-butylamino-6-(methylsulfonyl-methylamino)-isonicotinamide hydrochloride

Stir overnight at RT a solution of 2-sec-butylamino-6-(methylsulfonyl-methylamino)-pyridine-4-carboxylic acid (115 mg, 0.38 mmol), 3-(2-amino-1-hydroxy-3-phenylpropyl)-1-methylpiperazin-2-one (101 mg, 0.38 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (87.4 mg, 0.45 mmol), triethylamine (0.16 mL, 1.14 mmol) and 4-(dimethylamino)pyridine (4.6 mg, 0.04 mmol) in dichloromethane (10 mL). Dilute with more dichloromethane and wash with 5% aqueous sodium bicarbonate. Separate organic layer and wash with saturated aqueous sodium chloride, dry (magnesium sulfate concentrate and purify (silica gel chromatography, eluting with 9:1 dichloromethane:methanol) to give a white solid. Suspend the solid in 4 M HCl in 1,4-dioxane and stir for 10 min. Concentrate the solution to give the title compound as a yellow solid (Isomer 2, 47 mg, 21%).
MS (ES): m/z = 547 [M+H].

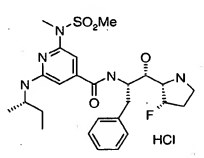
The compounds of EXAMPLE 9-15 may be prepared essentially essentially as described in EXAMPLE 8.

EX	Compound	MS [M+H]
9	N-[1-Benzyl-2-hydroxy-2-(4-methyl-3-oxopiperazin-2-yl)ethyl]-2-sec-butylamino-6-(methylsulfonyl-methylamino)-isonicotinamide hydrochloride Isomer 1	547
10	N-[1-Benzyl-2-hydroxy-2-(4-methyl-3-oxopiperazin-2-yl)ethyl]-2-sec-butylamino-6-(methylsulfonyl-methylamino)-isonicotinamide hydrochloride Isomer 3	547
11	N-[1-Benzyl-2-hydroxy-2-(4-methyl-3-oxopiperazin-2-yl)ethyl]-2-sec-butylamino-6-(methylsulfonyl-methylamino)-isonicotinamide hydrochloride Isomer 4	547
12	N-((1S,2R)-1-Benzyl-2-hydroxy-2-pyrrolidin-2-(R)-ylethyl)-2-(S)-sec-butylamino-6-methanesulfonyl-isonicotinamide hydrochloride	475
13	N-((1S,2R)-1-Benzyl-2-hydroxy-2-pyrrolidin-2-(R)-ylethyl)-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide	504

	hydrochloride	
14	N-((1S,2R)-1-Benzyl-2-hydroxy-2-(R)-pyrrolidin-2-ylethyl)-2-(methanesulfonyl-methylamino)-6-(methyl-propyl-amino)-isonicotinamide hydrochloride salt	504.3
15	N-[(1S,2R)-1-Benzyl-2-hydroxy-2-(R)-(2-pyrrolidinyl)-ethyl]-N´,N´-dipropyl-isophthalamide hydrochloride	452

EXAMPLE 16

2-(S)-(2-{[2-(S)-sec-Butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-1-(S)-hydroxy-3-phenylpropyl)-3-(S)-fluoropyrrolidine-1-carboxylic acid hydrochloride and 2-(S)-(2-{[2-(S)-sec-Butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-1-(S)-hydroxy-3-phenylpropyl)-3,3-difluoropyrrolidine-1-carboxylic acid hydrochloride



Dissolve a mixture of 2-(S)-(2-(S)-amino-1-(S)-hydroxy-3-phenylpropyl)-3-(S)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester and 2-(S)-(2-(S)-amino-1-(S)-hydroxy-3-phenylpropyl)-3,3-difluoropyrrolidine-1-carboxylic acid tert-butyl ester (822 mg, 2.43 mmol) in dichloromethane (10 mL). Add 2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinic acid potassium salt (822 mg, 2.43 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (512 mg, 2.67 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (361 mg, 2.67 mmol) and diisopropylethylamine (0.93 mL, 5.34 mmol). Stir the reaction for18 h at RT. Dilute the reaction with dichloromethane, wash with 5% aqueous potassium carbonate, dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 2:98 methanol:dichloromethane) to give the 2 separate title compounds (97mg and 32mg respectively).

MS (ES): m/z = 622.3 [M+H], MS (ES): m/z = 640.4 [M+H].

N-[1-Benzyl-2-(S)-(3-(S)-fluoropyrrolidin-2-yl)-2-(S)-hydroxyethyl]-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride

Add 4 M HCl in 1,4-dioxane (6 mL) to 2-(S)-(2-{[2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-1-(S)-hydroxy-3-phenylpropyl)-3-(S)-fluoropyrrolidine-1-carboxylic acid tert-butyl ester (97 mg, 0.16 mmol) and stir at RT for 20 min. Concentrate the reaction to give the title compound.
MS (ES): m/z = 522.2 [M+H].

N-[1-Benzyl-2-(S)-(3,3-difluoropyrrolidin-2-yl)-2-(S)-hydroxyethyl]-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride

Add 4 M HCl in 1,4-dioxane (5 mL) to 2-(S)-(2-{[2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-1-(S)-hydroxy-3-phenylpropyl)-3-difluoropyrrolidine-1-carboxylic acid tert-butyl ester (32 mg, 0.05 mmol) and stir at RT for 15 min. Concentrate the reaction to a residue and purify (silica gel chromatography, eluting with 4:96 methanol:dichloromethane) to give the title compound (18mg, 62%).
MS (ES): m/z = 540.3 [M+H].

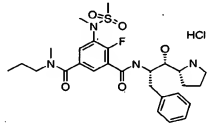
The compounds of EXAMPLE 17-20 may be prepared essentially as described in EXAMPLE 16.

EX	Compound	MS [M+H]
17	N-[1-(S)-Benzyl-2-(R)-hydroxy-2-(1,2,3,4-tetrahydro-isoquinolin-3-(R)-yl)-ethyl]-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride	666.3
18	2'-Fluorobiphenyl-3-carboxylic acid [1-(S)-benzyl-2-(R)-2-hydroxy (1,2,3,4-tetrahydroisoquinolin-3-(R)-yl)-ethyl]-amide hydrochloride	481.2
19	2-(2-{[2-sec-Butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-1-hydroxy-3-phenylpropyl)-6-ethylpiperidine-1-carboxylic acid hydrochloride-Isomer 2	546
20	2-(2-{[2-sec-Butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-1-hydroxy-3-phenylpropyl)-6-ethylpiperidine-1-carboxylic acid hydrochloride-Isomer 1	546
21	N-[(1S)-1-Benzyl-2-hydroxy-2-(6-methylpiperidin-2-yl)-ethyl]-2-sec-	532

	butylamino-6-(methanesulfonyl-methyl-amino)-isonicotinamide hydrochloride-Isomer 1	
22	N-[(1S)-1-Benzyl-2-hydroxy-2-(6-methylpiperidin-2-yl)-ethyl]-2-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide hydrochloride-Isomer 2	532

EXAMPLE 23

N^3-((1S,2R)-1-Benzyl-2-hydroxy-2-(R)-pyrrolidin-2-ylethyl)-4-fluoro-5-(methanesulfonyl-methylamino)-N^1-methyl-N^1-propyl-isophthalamide hydrochloride



Dissolve 6-fluoro-5-(methanesulfonyl-methylamino)-N-methyl-N-propyl-isophthalamic acid (102 mg, 0.294 mmol), O-benzotriazol-1-yl-tetramethyluronium hexafluorophosphate (123 mg, 0.324 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (49.6 mg, 324 mmol) and diisopropylethylamine (102.76 µL, 0.589 mmol) in DMF (3.00 mL). Stir for 30 min. Add (R)-2-((1S,2S)-2-amino-1-hydroxy-3-phenylpropyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and stir at RT for 4 h. Add 10% aqueous potassium carbonate solution (10 mL) and extract with ethyl acetate (2 x 50 mL). Combine the organic layers, wash with 1 N lithium chloride solution (25 mL), saturated aqueous sodium chloride solution (25 mL), dry (magnesium sulfate) concentrate and purify (silica gel chromatography, eluting with 2.5:97.5 methanol:ethyl acetate) to give the desired tert-butyl carbamate intermediate as a white foam. Dissolve the purified material in a 20:1 diethyl ether:methanol mixture (2.1 mL) and add 1 N HCl in diethyl ether solution (4.1 mL) and stir overnight. Concentrate the reaction mixture to dryness to give the title compound as a white solid (120 mg, 70%).

MS (ES): m/z = 549.2 [M+H].

EXAMPLE 24

N-[(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-(R)-piperidin-2-ylethyl]-acetamide

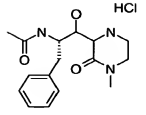
Dissolve (R)-2-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-piperidine-1-carboxylic acid tert-butyl ester (0.085 g, 0.21 mmol) in hydrogen chloride (4 M in 1,4-dioxane, 3 mL). Stir 1 h and concentrate to give the title compound as a foam (0.077 g, 100%).

MS (ES): $m/z = 313.2$ [M+H].

The compounds of EXAMPLES 25-31 may be prepared essentially as described in EXAMPLE 24.

EX	Compound	MS [M+H]
25	N-((1S,2R)-1-Benzyl-2-hydroxy-2-(R)-piperidin-2-ylethyl)-acetamide hydrochloride	277.2
26	N-[(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-(R)-pyrrolidin-2-yl-ethyl]-acetamide hydrochloride	299.3
27	Toluene-4-sulfonic acid (3R,5R)-5-((1R,2S)-2-acetylamino-1-hydroxy-3-phenylpropyl)-pyrrolidin-3-yl ester hydrochloride	433.3
28	N-[(1S,2R)-1-(3,5-Difluorobenzyl)-2-((S)-4-fluoropyrrolidin-2-yl)-2-hydroxyethyl]-acetamide hydrochloride	317.3
29	N-[(1S,2R)-1-Benzyl-2-hydroxy-2(R)-(2-pyrrolidinyl)-ethyl]-isonicotinamide bishydrochloride	426
30	N-[2-(2-Azabicyclo[2.2.1]hept-3-yl)-1-benzyl-2-hydroxyethyl]-acetamide trifluoroacetate-Isomer 1	289.2
31	N-[2-(2-Azabicyclo[2.2.1]hept-3-yl)-1-benzyl-2-hydroxyethyl]-acetamide trifluoroacetate-Isomer 2	289.2

EXAMPLE 32



N-[1(S)-Benzyl-2-hydroxy-2-(4-methyl-3-oxopiperazin-2-yl)-ethyl]-acetamide hydrochloride

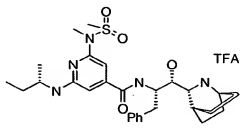
Stir overnight at RT under a nitrogen atmosphere a solution of acetic acid (25 µl, 0.45), 3-(2(S)-amino-1-hydroxy-3-phenylpropyl)-1-methylpiperazin-2-one (120 mg, 0.45 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (112 mg, 0.58 mmol), triethylamine (0.12 mL, 0.9 mmol), dimethylaminopyridine (5.5 mg, 0.04 mmol) and 1-hydroxybenzotriazole hydrate (HOBt) (79 mg, 0.58 mmol) in dichloromethane (10mL/mmol). Dilute with more dichloromethane and wash with 5% aqueous sodium bicarbonate solution, saturated aqueous sodium chloride. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 9:1 dichloromethane:methanol) to provide a white solid. Suspend the solid in 4 M HCl in 1,4-dioxane and stir for 10 min and concentrate the solution to give the title compound as a white solid (15 mg, 10%).

The compounds of EXAMPLES 33-36 may be prepared essentially as described in EXAMPLE 32.

EX	Compound	MS [M+H]
33	N-[(1S)-1-Benzyl-2-(6-ethylpiperidin-2-yl)-2-hydroxyethyl]-acetamide hydrochloride-Isomer 1	305
34	N-[(1S)-1-Benzyl-2-(6-ethylpiperidin-2-yl)-2-hydroxyethyl]-acetamide hydrochloride-Isomer 2	305
35	N-[(1S)-1-Benzyl-2-hydroxy-2-(6-methylpiperidin-2-yl)-ethyl]-acetamide hydrochloride-Isomer 1	291
36	N-[(1S)-1-Benzyl-2-hydroxy-2-(6-methylpiperidin-2-yl)-ethyl]-acetamide hydrochloride-Isomer 2	291

EXAMPLE 37

N-{2-[2-Aza-bicyclo[2.2.2]octyl]-benzyl-2-hydroxyethyl}-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide trifluoroacetate-Isomer 1



3-(2-{[2-(S)-sec-Butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-1-hydroxy-3-phenylpropyl)-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester-Isomer 1

Dissolve 2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinate potassium salt (47 mg, 0.138 mmol) in THF (2 mL) at RT. Add 1-hydroxy-7-azabenzotriazole (HOAt) (0.5 M in DMF, 0.28 mL,) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (27 mg, 0.138 mmol) to the solution. After 10 min add 3-[2-amino-1-hydroxy-3-phenylpropyl]-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester-Isomer 1 (50 mg, 0.14 mmol) to the reaction and stir at RT overnight. Quench the reaction by saturated aqueous sodium bicarbonate solution and dilute with dichloromethane. Extract the organic layer and wash with saturated aqueous sodium chloride solution, dry (magnesium sulfate), filter and concentrate to give the crude title compound which is used in the next step without further purification.

N-{2-[2-Aza-bicyclo[2.2.2]octyl]-benzyl-2-hydroxyethyl}-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide trifluoroacetate-Isomer 1

Dissolve 3-(2-{[2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-pyridine-4-carbonyl]-amino}-1-hydroxy-3-phenylpropyl)-2-aza-bicyclo[2.2.2]octane-2-carboxylic acid tert-butyl ester (87 mg, 0.14 mmol) in THF (3 mL) at 0 °C and add dropwise 4 N HCl in 1,4-dioxane (0.17 mL, 0.67 mmol). Stir the mixture from 0 °C to RT overnight. Concentrate most solvent and excess HCl and purify (reverse phase

HPLC, gradient of water and acetonitrile with 1% trifluoroacetic acid buffer) to give the title compound .

MS (ES): *m/z* = 544.3 [M+H], MS (ES): *m/z* = 656.3 [M-H·TFA].

The compounds of EXAMPLE 38-40 may be prepared essentially as described in EXAMPLE 37.

EX	Compound	MS [M+H]
38	N-[2-[2-Aza-bicyclo[2.2.2]oct-yl]-benzyl-2-hydroxyethyl]-2-(S)-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide trifluoroacetate-Isomer 2	544.3
39	N-[2-(2-Aza-bicyclo[2.2.1]hept-3-yl)-1-benzyl-2-hydroxyethyl]-2-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide trifluoroacetate-Isomer 1	530.3
40	N-[2-(2-Aza-bicyclo[2.2.1]hept-3-yl)-1-benzyl-2-hydroxyethyl]-2-sec-butylamino-6-(methanesulfonyl-methylamino)-isonicotinamide trifluoroacetate-Isomer 2	530.3

EXAMPLE 41

N-((1S,2R)-2-Homopiperidin-2-yl-1-benzyl-2-hydroxy-ethyl)-2-((S)-sec-butylamino)-6-(methanesulfonyl-methyl-amino)-isonicotinamide hydrochloride (Isomer 1)

Dissolve 2-((S)-sec-Butylamino)-6-(ethyl-methyl-amino)-isonicotinic acid (2.5 mg, 0.007 mmol) in a 1:1:5 mixture of tert-butanol:acetonitrile:dichloromethane (0.5 ml). Add 1-hydroxybenzotriazole (4.2 mg, 0.01 mmol) followed by 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (1.92 mg, 2.05 mmol). Add dropwise to a solution of (1S,2R)-1-Homopiperidin-2-yl-2-dibenzylamino-3-phenyl-propan-1-ol (Isomer 1) (7 mg, 0.03 mmol) and triethylamine (12 ul, 0.09 mmol) in the solvent mixture (0.5 ml) with rapid stirring over 10 minutes at room temperature. Add 2 mL dichloromethane, extract with water (2 ml), saturated aqueous sodium bicarbonate (3 ml), saturated aqueous sodium chloride (3 ml), and dry (sodium sulfate), filter, and concentrate under reduced pressure. Purify using HPLC_MS to isolate product (19x300 mm, 7µm, C-18 column; flow rate = 20 mL/min; mobile phase gradient 5%-95% over 26 minutes; Solvent A: acetonitrile; Solvent B: 0.1% trifluoroacetic acid in water). Add 1 ml of ethyl acetate and 0.01 ml of 1 N HCl in diethyl ether. Evaporate the solvent to obtain the product (4 mg, 0.83 mmol, 95% yield). MS (ESI) *m/z* 532.3 (M+H).

The compound of EXAMPLE 42 may be prepared essentially as described in EXAMPLE 41.

EX	Compound	MS [M+H]
42	N-((1S,2R)-2-Homopiperidin-2-yl-1-benzyl-2-hydroxy-ethyl)-2-((S)-sec-butyl-amino)-6-(methanesulfonyl-methyl-amino)-isonicotinamide hydrochloride (Isomer 2)	532.3

The compounds of Formula I are inhibitors of BACE and thereby inhibit the production of A-β peptide which has been implicated in the pathology and progression of a number of neurodegenerative disorders, including Alzheimer's disease (See: Varghese, et al., Journal of Medicinal Chemistry, **46**(22), 4625 (2003)). Methods for determining the BACE inhibitory activity of compounds are well known in the art (See: Sinha, et al., Science, **286**, 735 (1999); Turner, et al., Biochemistry, **40**, 10001 (2001); Hom, et al., Journal of Medicinal Chemistry, **46**, 1799 (2003); US #5,744,346; US #5,942,400; WO00/17369; WO00/03819; WO 03/040096; and WO 04/024081).

In vitro Assay Procedures:

For in vitro enzymatic and cellular assays, test compounds are prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted (in a 1:3, 1:2.5, 1:2, or 1:1 dilution series) in DMSO to obtain a final compound concentration of 10 millimolar to 1 micromolar at the first highest concentration of a ten-point dilution curve in a 96-well round-bottom plate right before conducting the in vitro enzymatic and whole assays.

In vitro protease inhibition assays:

BACE1 mcaFRET Assay

Serial dilutions of test compounds are prepared as described above. Two microliter of each dilution is added to each well on row A to H of a corresponding low protein binding black plate to which 50 microliter of 50 millimolar ammonium acetate, pH 4.6, 1 mM Triton X-100, 1mg/ml Bovine Serum Albumin, and 15 micromolar of FRET substrate (sequence: (MCA)-S-E-V-N-L-D-A-E-F-R-K(Dnp)-R-R-R-R-NH_2) for

BACE1 activity are pre-added. The content is mixed well on a plate shaker for 10 min. Fifty microliter of two hundred picomolar human BACE1(1-460):Fc (See: Vasser, et al., Science, **286**, 735-741 (1999)) in the same reaction buffer described above is added to the plate containing substrate and test compounds to initiate the reaction. The relative fluorescence unit (RFU) of the mixture at time 0 is recorded at excitation wavelength 330nm and emission wavelength 400nm, after brief mixing on a plate shaker. The reaction plate is covered with aluminum foil and kept in a dark humidified oven at room temperature for 16 to 24 hours. The RFU at the end of incubation is recorded with the same excitation and emission setting. The difference of the RFU at time 0 and the end of incubation represents the activity of BACE1 under the compound treatment. The 10-point inhibition curve was plotted and fitted with the four-parameter logistic equation to obtain the EC_{50} and IC_{50} values. (See: Sinha, et al., Nature, **402**, 537-540 (2000)). Representative compounds of Formula I were tested essentially as described above and exhibited an IC_{50} for BACE1 of at least 15μM.

BACE2 mcaFRET Assay

Serial dilutions of test compounds are prepared as described above. Two microliter of each dilution is added to each well on row A to H of a corresponding low protein binding black plate to which 50 microliter of 50 millimolar ammonium acetate, pH 4.6, 1 mM Triton X-100, 1mg/ml Bovine Serum Albumin, and 15 micromolar of FRET substrate (sequence: (MCA)-S-E-V-N-L-D-A-E-F-R-K(Dnp)-R-R-R-R-NH_2) for BACE2 activity are pre-added. The content is mixed well on a plate shaker for 10 min. Fifty microliter of four hundred picomolar purified recombinant human BACE2(1-460):Fc in the same reaction buffer described above is added to the plate containing substrate and test compounds to initiate the reaction. The relative fluorescence unit (RFU) of the mixture at time 0 is recorded at excitation wavelength 330nm and emission wavelength 400nm, after brief mixing on a plate shaker. The reaction plate is covered with aluminum foil and kept in a dark humidified oven at room temperature for 16 to 24 hours. The RFU at the end of incubation is recorded with the same excitation and emission setting. The difference of the RFU at time 0 and the end of incubation represents the activity of BACE2 under the compound treatment. The 10-point inhibition

curve was plotted and fitted with the four-parameter logistic equation to obtain the EC_{50} and IC_{50} values. Representative compounds of Formula I were tested essentially as described above and exhibited an IC_{50} for BACE2 of at least 15μM.

Expression of human and murine BACE1.

Both human (accession number: AF190725) and murine (accession number: NM_011792) BACE1 were cloned from total brain cDNA by RT-PCR. The nucleotide sequences corresponding to amino acid sequences #1 to 460 were inserted into the cDNA encoding human IgG_1 (Fc) polypeptide (Vassar et al. 1999). This fusion protein of BACE1(1-460) and human Fc, named *hu*BACE1:Fc, was constructed into the pJB02 vector. Human BACE1(1-460):Fc (*hu*BACE1:Fc) and murine BACE1(1-460):Fc (*mu*BACE1:Fc) were transiently expressed in HEK293 cells. 250 μg cDNA of each construct was mixed with Fugene 6 and added to 1 liter HEK293 cells. Four days after the transfection, conditioned media were harvested for purification.

Purification of huBACE1:Fc and muBACE1:Fc.

Conditioned media of HEK293 cell transiently transfected with *hu*BACE1:Fc or *mu*BACE1:Fc cDNA were collected. Cell debris was removed by filtering the conditioned media through 0.22 μm sterile filter. 5 ml Protein A-agarose (bed volume) was added to 4 liter conditioned media. This mixture was gently stirred overnight at 4° C. The Protein A-agarose resin was collected and packed into a low-pressure chromatography column. The column was washed with 20X bed volumes of PBS at flow rate 20 ml per hour. Bound *hu*BACE1:Fc or *mu*BACE1:Fc protein was eluted with 50 mM acetic acid, pH 3.6, at flow rate 20 ml per hour. 1 ml fractions of eluate were neutralized immediately with 0.5 ml 200 mM ammonium acetate, pH 6.5. The purity of final product was assessed by electrophoresis in 4-20% Tris-Glycine SDS-PAGE. The enzyme was stored at –80C in small aliquots.

Whole cell assay for measuring the Inhibition of Beta-Secretase Activity

The routine whole cell assay for the measurement of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEK293p (ATCC Accession No. CRL-1573) stably expressing a human APP751 cDNA containing the naturally occurring

double mutation Lys651Met52 to Asn651Leu652, commonly called the Swedish mutation (noted HEK293/APP751sw) and shown to overproduce Abeta (Citron et al., 1992, *Nature* 360:672-674). Human embryonic kidney HEK293p cells stably expressing wild-type human APP751 cDNA (noted HEK293/APP751wt) are also used to assess the inhibition of beta-secretase activity. ***In vitro*** Aβ reduction assays have been described in the literature (See: Dovey, et al., Journal of Neurochemistry, **76**, 173-181 (2001); Seubert, et al., Nature, **361**, 260 (1993); and Johnson-Wood, et al., Proc. Natl. Acad. Sci. USA, **94**, 1550-1555 (1997))

Cells (HEK293/APP751sw or HEK293/APP751wt, at $3x10^4$ cells/well, containing 200 microliters culture media, DMEM containing 10% FBS) are incubated at 37C for 4 to 6 hours in the presence/absence of inhibitors (diluted in DMSO) at the desired concentration. At the end of the incubation, conditioned media are analyzed for beta-secretase activity, for example, by analysis of cleavage fragments, Abeta peptide and sAPPbeta. Abeta peptides are measured by a sandwich ELISA, using monoclonal 266 as a capture antibody and biotinylated 3D6 as reporting antibody. The sAPPbeta fragments are analyzed by a sandwich ELISA, using monoclonal 8E5 antibody as a capture antibody and rabbit polyclonal 192sw or 192wt as a reporting antibody. Note that sAPPbeta is the cleavage product of full length APP by BACE1. The concentration of sAPPbeta released in the conditioned media following the compound treatment corresponds to the activity of BACE1 under such conditions. The 10-point inhibition curve was plotted and fitted with the four-parameter logistic equation to obtain the EC_{50} and IC_{50} values for the Abeta, sAPPbeta-lowering effect.

***In vivo* Inhibition of Beta-Secretase**

Several animal models, including mouse, guinea pig, dog, and monkey, may be used to screen for inhibition of beta- secretase activity in vivo following compound treatment. Animals used in this invention can be wild type, transgenic, or gene knockout animals. For example, the PDAPP mouse model, prepared as described in Ganes et al., 1995, *Nature* 373:523-527, and other non-transgenic or gene knockout animals are useful to analyze in vivo inhibition of Abeta and sAPPbeta production in the presence of inhibitory compounds. Generally, 4 to 12 month old PDAPP mice, gene knockout mice or non-transgenic animals are administered compound formulated in vehicles, such as corn oil, cyclodextran, phosphate buffers, Pharmasolve, or other suitable vehicles. One to twenty-four hours following the administration of compound, animals are sacrificed, and brains as well as plasma are removed for analysis of Abeta and sAPP fragments. (See: Dovey, et al., Journal of Neurochemistry, **76**, 173-181 (2001); and Johnson-Wood, et al., Proc. Natl. Acad. Sci. USA, **94**, 1550-1555 (1997))

Beginning at time 0, brain tissue, plasma or cerebrospinal fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including Abeta peptides, sAPPbeta and other APP fragments, for example, by specific sandwich ELISA assays. At the end of the test period, animals are sacrificed and brain tissues, plasma or cerebrospinal fluid are analyzed for the presence of Abeta peptide and sAPPbeta. Brain tissues of APP transgenic animals are also analyzed for the amount of beta-amyloid plaques following compound treatment.

Animals (PDAPP or other APP transgenic mice) administered an inhibitory compound may demonstrate the reduction of Abeta or sAPPbeta in brain tissues, plasma or cerebrospinal fluids and decrease of beta amyloid plaques in brain tissue, as compared with vehicle-treated controls. Animals (PDAPP or other APP transgenic mice) administered the inhibitory compounds of the invention may also show improvement in cognitive behavioral assessments for learning and memory tasks.

Oral administration of the compounds of the present invention is preferred. However, oral administration is not the only route or even the only preferred route. For

example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine, and the intravenous route may be preferred as a matter of convenience or to avoid potential complications related to oral administration. Compounds of Formula I may also be administered by the percutaneous, intramuscular, intranasal or intrarectal route in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs, the convenience of the patient and the caregiver, and other relevant circumstances (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material that can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations of the present invention may be determined by methods well known to the skilled artisan.

The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as povidone, hydroxypropyl cellulose, microcrystalline cellulose, or gelatin; excipients or diluents such as: starch, lactose, microcrystalline cellulose or dicalcium phosphate, disintegrating agents such as: croscarmellose, crospovidone, sodium starch glycolate, corn starch and the like; lubricants such as: magnesium stearate, stearic acid, talc or hydrogenated vegetable oil; glidants such as colloidal silicon dioxide; wetting agents such as: sodium lauryl sulfate

and polysorbate 80; and sweetening agents such as: sucrose, aspartame or saccharin may be added or a flavoring agent such as: peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, hydroxypropyl methylcellulose, polymethacrylates, or other coating agents. Syrups may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

The compounds of Formula I are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.0001 to about 30 mg/kg of body weight. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

In order to achieve or maintain appropriate levels of the compounds of Formula I in the brain of an afflicted mammal, it may be necessary or desirable to co-administer an effective amount of an inhibitor of P-glycoprotein (P-gp). P-gp inhibitors and the use of such compounds are known to those skilled in the art. (See: Cancer Research, **53**, 4595 (1993); Clin. Cancer Res., **2**, 7 (1996); Cancer Research, **56**, 4171 (1996); WO99/64001; and WO01/10387).

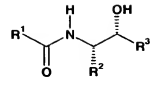
The P-gp inhibitor may be administered in any manner that achieves a sufficient degree of inhibition of P-gp to achieve or maintain sufficient levels of the compounds of Formula I for effective BACE inhibition in the brain of an afflicted mammal. As such, the P-gp inhibitor may be administered separately before, during, or after the administration of a compound of Formula I. Furthermore, if desirable, the

P-gp inhibitor may be formulated with a compound of Formula I. These formulations and methods represent further embodiments of the present invention.

Many suitable P-gp inhibitors are known today and undoubtably others will be identified in the future. Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10, 11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY355979, PSC-833, GF-102,918 and other steroids.

We Claim:

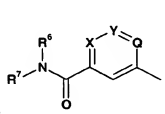
1. A compound of Formula I:



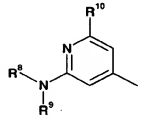
I

where:

R^1 is hydrogen, $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_1\text{-}C_6$ alkyl), $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkenyl), $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkynyl), $C_3\text{-}C_7$ cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, $C_1\text{-}C_6$ alkoxy, $C_3\text{-}C_7$ cycloalkoxy, and NR^4R^5, or



or



;

R^1 is

R^2 is $C_1\text{-}C_3$ alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

R^3 is piperidin-2-yl optionally substituted with one or two substituents independently selected from $C_1\text{-}C_6$ alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and $C_1\text{-}C_6$ alkyl, 1-($C_1\text{-}C_6$ alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydro-isoquinolin-3-yl optionally substituted with one or two substituents selected from halo and $C_1\text{-}C_6$ alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo, or one or two substituents selected from hydroxy and fluoro;

X is CH, N, or $N^+\text{-}O^-$;

Y is CR^{11}, N, or $N^+\text{-}O^-$;

Q is CR^{12}, N, or $N^+\text{-}O^-$;

R^4 is hydrogen, $C_1\text{-}C_6$ alkyl, or phenyl;

R^5 is hydrogen, C_1-C_6 alkyl, phenyl, -C(O)(C_1-C_6 alkyl), or $-SO_2$(C_1-C_6 alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or C_1-C_6 alkyl;

R^9 is C_3-C_5 cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1-2}R^{16}$, $-NR^{17}SO_2R^{18}$, (C_1-C_3 alkoxy)-carbonyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with C_1-C_3 alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}; CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

R^{23} is hydrogen or methyl;

R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

R^{26} is methyl; or

R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring;

or a pharmaceutically acceptable salt thereof; provided that no more than one of X, Y, and Q may be N or N^{+}-O^{-}.

2. A method of treating Alzheimer's disease in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

3. A method of preventing the progression of mild cognitive impairment to Alzheimer's disease in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

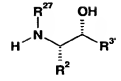
4. A method of inhibiting BACE in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

5. A method for inhibiting β-secretase mediated cleavage of amyloid precursor protein comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

6. A method for the inhibition of production of A-β peptide comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

7. A pharmaceutical formulation comprising a compound of Formula I, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

8. A compound of Formula II:



II

where:

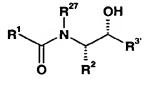
R^2 is C_1-C_3 alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

R^{27} is either hydrogen or a nitrogen protecting group;

$R^{3'}$ is piperidin-2-yl optionally substituted with one or two substituents independently selected from C_1-C_6 alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and C_1-C_6 alkyl, 1-(C_1-C_6 alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydro-isoquinolin-3-yl optionally substituted with one or two substituents selected from halo and C_1-C_6 alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo or one or two substituents selected from hydroxy and fluoro; all substituted on the ring nitrogen adjacent to the point of attachment with variable R^{28};

R^{28} is either hydrogen or a nitrogen protecting group; or an acid addition salt thereof.

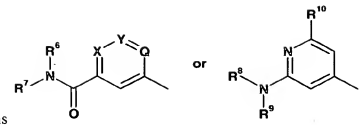
9. A compound of Formula III:



III

where:

R^1 is hydrogen, (C_3-C_7 cycloalkyl)$_{0-1}$(C_1-C_6 alkyl), (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkenyl), (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl each optionally substituted with one or two oxo groups or optionally substituted with up to three groups independently selected from the group consisting of halo, hydroxy, thiol, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, and NR^4R^5, or



R^1 is

R^2 is C_1-C_3 alkyl or benzyl optionally mono- or difluorinated in the phenyl ring;

$R^{3'}$ is piperidin-2-yl optionally substituted with one or two substituents independently selected from C_1-C_6 alkyl, pyrrolidin-2-yl optionally substituted with p-toluenesulfonyloxy or with one or two substituents independently selected from halo and C_1-C_6 alkyl, 1-(C_1-C_6 alkyl)piperazin-2-on-3-yl, homopiperidin-2-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl optionally substituted with one or two substituents selected from halo and C_1-C_6 alkyl, 2-azabicyclo[2.2.2]oct-(5Z)ene-3-yl, 2-azabicyclo[2.2.1]hept-3-yl, or 2-azabicyclo[2.2.2]oct-3-yl optionally substituted with oxo or one or two substituents selected from hydroxy and fluoro; all substituted on the ring nitrogen adjacent to the point of attachment with variable R^{28};

X is CH, N, or N^+-O^-;

Y is CR^{11}, N, or N^+-O^-;

Q is CR^{12}, N, or N^+-O^-;

R^4 is hydrogen, C_1-C_6 alkyl, or phenyl;

R^5 is hydrogen, C_1-C_6 alkyl, phenyl, -C(O)(C_1-C_6 alkyl), or $-SO_2$(C_1-C_6 alkyl);

R^6 and R^7 are independently selected from the group consisting of methyl, ethyl, and propyl;

R^8 is hydrogen or C_1-C_6 alkyl;

R^9 is C_3-C_5 cycloalkyl, sec-butyl, or $-CH_2R^{13}$;

R^{10} is $-CF_2R^{14}$, $-OR^{15}$, $-CH_2C(O)CH_3$, $-S(O)_{1\text{-}2}R^{16}$, $-NR^{17}SO_2R^{18}$, (C_1-C_3 alkoxy)-carbonyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl, or tetrazol-5-yl optionally substituted with C_1-C_3 alkyl;

R^{11} is hydrogen, chloro, isobutyl, CH_2R^{19}; CF_2R^{20}, 1,1,1-trifluoro-2-hydroxyeth-2-yl, C_2-C_4 alkenyl optionally substituted with one or two fluorine atoms, OR^{21}, $C(O)R^{22}$, N(methyl)(methylsulfonyl), N(methyl)(acetyl), pyrrolidin-2-on-1-yl, methylsulfonyl, N,N-dimethylaminosulfonyl, phenyl optionally substituted with one or two substituents selected from the group consisting of hydroxymethyl, methoxy, fluoro, and

methylsulfonyl, 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl, 1,3-oxathiolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithian-2-yl, pyridinyl, thiazolyl, oxazolyl, or 1,2,4-oxadiazolyl optionally substituted with methyl;

R^{12} is hydrogen or fluoro;

R^{13} is ethynyl or cyclopropyl;

R^{14} is hydrogen or methyl;

R^{15} is difluoromethyl or methanesulfonyl;

R^{16} is C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or $-NR^{25}R^{26}$;

R^{17} is hydrogen, C_1-C_3 alkyl optionally substituted with up to 3 fluorine atoms, or C_3-C_6 cycloalkyl;

R^{18} is C_1-C_3 alkyl or C_3-C_6 cycloalkyl;

R^{19} is fluoro, hydroxy, or C_1-C_3 alkoxy;

R^{20} is hydrogen, phenyl, or furyl;

R^{21} is C_1-C_3 alkyl optionally substituted with one or two fluorine atoms;

R^{22} is C_1-C_3 alkyl, C_3-C_5 cycloalkyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, $NR^{23}R^{24}$, pyrrolidin-1-yl optionally substituted with methyl or one or two fluorine atoms, piperidin-1-yl, phenyl, pyridinyl, or furyl;

R^{23} is hydrogen or methyl;

R^{24} is methyl, ethyl, or propyl;

R^{25} is hydrogen or methyl;

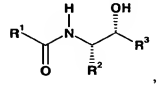
R^{26} is methyl; or

R^{25} and R^{26} taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring;

R^{27} and R^{28} are either independently a nitrogen protecting group or one is hydrogen and the other a nitrogen protecting group; or an acid addition salt thereof provided that no more than one of X, Y, and Q may be N or N^+-O^-.

ABSTRACT

The present invention provides BACE inhibitors of Formula I:



I

methods for their use and preparation, and intermediates for their preparation.